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TABLE OF CONTENTS

Evolution of Rheumatic Heart Disease in Children
JOINT REPORT BY MEDICAL RESEARCH COUNCIL AND AMERICAN HEART ASSOCIATION 1033

Disinfection of the Skin of Operation Sites
E. J. L. LOWBURY, D.M., H. A. LILLY, F.I.M.L.T., and J. P. BULL, M.D. 1039

Hydroflumethiazide Diuresis in Hospitalized Patients
GEORGE A. PORTER, M.D., and NORMAN A. DAVID, M.D. 1044

Sympathetic Blockade in Treatment of Hypertension
CLIFTON P. LOWTHER, M.B., F.R.F.P.S., M.R.C.P.Ed., and RICHARD W. D. TURNER, M.D., F.R.C.P., F.R.C.P.Ed. 1049

Cerebrospinal Fluid Gamma-globulin in Multiple Sclerosis
E. J. FIELD, M.D., M.S., Ph.D., and ALAN RIDLEY, M.B., M.R.C.P. 1053

Trichophyton Sulphureum in a Residential School
D. W. R. MACKENZIE, Ph.D., B.Sc., D. BURROWS, M.D., and A. L. WALBY, M.B., D.P.H. 1055

Control of Degree of Oxygenation During Total Body Perfusion
D. RACE, M.B., and J. W. W. THOMSON, M.B., F.R.C.S.Ed. 1058

Aetiology of Congenital Talipes W. A. CRABBE, F.R.C.S. 1060

Hypernephroma and Polycythaemia AAGE DRIVSHOLM, M.D. 1063

Successful Maintenance of Pernicious Anaemia Patients with Vitamin B_{12} and Intrinsic Factor for Long Periods LEON ELLENBOGEN, Ph.D., WILLIAM L. WILLIAMS, Ph.D., and HERBERT C. LICHTMAN, M.D. 1066

MEDICAL MEMORANDA

Alveolar Soft Part Sarcoma. M. FARQUHARSON, M.D., M.R.C.P. 1068

BOOK REVIEWS 1070

GENERAL ARTICLES AND NEWS

Biology of Space Travel 1079
Accident Management and General Practice 1080
To-day's Drugs 1084
FORENSIC PATHOLOGY AND MEDICINE 1081
CHILD NEUROLOGY AND CEREBRAL PALSY 1082
HISTORY OF MEDICAL PRACTICE IN BRITAIN 1083
OBITUARY 1094
VITAL STATISTICS 1098
MEDICAL NEWS 1100
BIRTHS, MARRIAGES, AND DEATHS 1101

QUESTIONS AND COMMENTS

Sliding Hiatus Hernia—First-aid for Patients on Anticoagulants—Collapse after Gold Injection—Buerger's Disease in a Woman 1102

LEADING ARTICLES

Rheumatic Heart Disease in Children 1073
Steatorrhoea 1074
Package Deal Completed 1075

ANNOTATIONS

Dental Implants 1076
Smoking and Disease 1077
Clinical Discussions in B.M.A. House 1077
New Chair of Child Health 1078
Safety in Gas Cookers 1078
New Chief Medical Officer 1078

CORRESPONDENCE

Faulty Anaesthetic Apparatus. PHILIP AYRE, F.F.A. R.C.S. 1084
"Celbenin"-resistant Staphylococci. R. KNOX, M.D., F.R.C.P.; G. T. STEWART, M.D. 1085

SUPPLEMENT

Full Contents on First Page of Supplement
Special Representative Meeting 131
Special Conference of L.M.C.s 147
Inquiry into Alleged Irregular Charges 158
Correspondence:
Hospital Authorities. K. W. MONSARRAT, F.R.C.S.Ed. 160

CORRESPONDENCE—*contd.*

Mode of Action of "Celbenin." W. B. HUGO, Ph.D., and A. D. RUSSELL, B.Pharm. 1085
Metronidazole in Trichomoniasis. WILFRID MILLS, F.R.C.O.G. 1085
New Rashes for Old. ANDREW SMITH, M.B., and others 1086
Potassium Perchlorate in Thyrotoxicosis. M. E. MORGANS, M.D., and W. R. TROTTER, D.M. 1086
Hypophysectomy in Breast Cancer. J. D. N. NABARRO, M.D., F.R.C.P. 1087
Medical Practice Centre. R. LAW, M.B. 1087
Our Hospitals. EVELYN M. ASBUTHNOT, M.B. 1088
Central Sterile Supply Departments. E. F. WILSON, F.R.C.S.; E. J. O'MULLANE, F.F.A. R.C.S., and A. J. OGG, F.R.C.S. 1088
Emergency Supplies Room. D. W. A. MCCREADIE, L.R.C.P.Ed. 1089
Resuscitation Apparatus. G. L. ZEITLIN, M.B. 1089
Intra-articular Steroids. F. G. WARD, F.R.C.S. 1089
Suppuration in Rheumatoid Arthritis. M. V. WELLS, M.B. 1089
Letters on other subjects on pp. 1090–4

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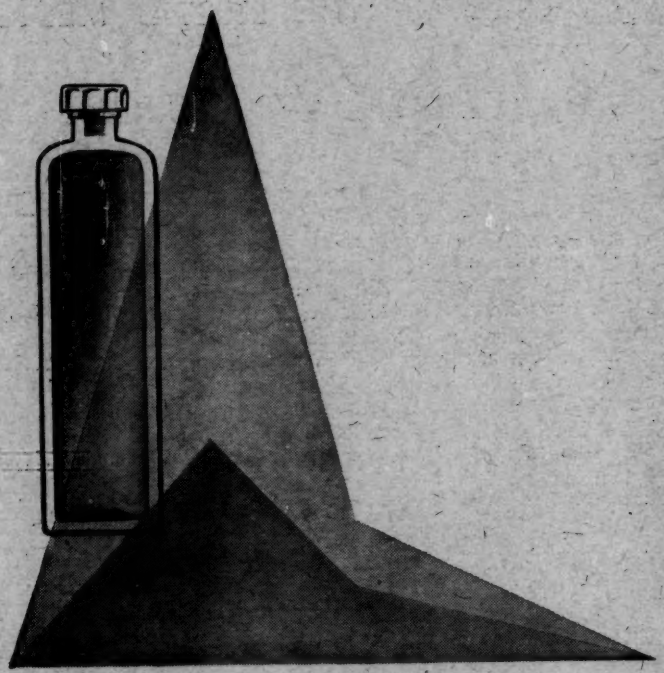

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 8 1960

EVOLUTION OF RHEUMATIC HEART DISEASE IN CHILDREN

Five-Year Report of a Co-operative Clinical Trial of A.C.T.H., Cortisone, and Aspirin

A JOINT REPORT* BY

THE RHEUMATIC FEVER WORKING PARTY OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN

AND

THE SUBCOMMITTEE OF PRINCIPAL INVESTIGATORS OF THE AMERICAN COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE, AMERICAN HEART ASSOCIATION

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Statistical consultation and services were provided by Miss MARJORIE T. BELLOWS, chief statistician, and Mrs. ELIZABETH R. DENSEN, of the American Heart Association, and Dr. JOHN KNOWELDEN, London School of Hygiene and Tropical Medicine. Mr. FELIX MOORE, professor and chairman, Department of Public Health Statistics, University of Michigan School of Public Health, served as statistical consultant. Dr. A. ST. J. DIXON, Taplow, served as co-ordinating registrar for the British centres. Mrs. RUTH E. RUTSTEIN was co-ordinator for the centres in the United States.

The United Kingdom and United States co-operative clinical trial was set up in 1951–2 to compare the relative merits of A.C.T.H., cortisone, and aspirin in the treatment of rheumatic fever and the prevention of rheumatic heart disease. Over a period of approximately a year and a half, and under closely defined diagnostic criteria, 497 children under the age of 16 were admitted to the trial in 12 centres in the United Kingdom, the United States, and Canada. These patients were allocated at random to one or another of the three treatments under investigation. They were treated according to a specified plan for six weeks, and after a further three weeks of detailed observation were followed up at defined intervals. Full details of the plan of the study have been given in an earlier publication.[1]

The previous report compared the three treatment groups in detail throughout the six weeks of treatment, three succeeding weeks of observation, and at the end of a further year of follow-up. It was concluded that there was no evidence that any of the three agents resulted in uniform termination of the disease, and on all treatments some patients develop fresh manifestations during treatment. Treatment with either of the hormones had resulted in more prompt control of certain acute manifestations, but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones was followed by a more rapid disappearance of nodules and soft apical systolic murmurs. At the end of one year, however, there was no significant difference among the three treatment groups in the status of the heart.

This second joint report records the state of the patients after a follow-up of five years. It is concerned with a comparison of the amount and severity of rheumatic heart disease in each of the three treatment groups at the end of this time period. It also demonstrates that the status of the heart at the start of treatment is the major factor determining the condition of the heart at the end of five years and that no treatment can be properly evaluated if this factor is not taken closely into account.

The Numbers Involved

Of the 497 cases admitted to the trial (240 U.K. and 257 U.S.) 445 (89.5%) were known to be alive at the end of the five years, and the status of the heart had been recorded for all but 19 of them. Sixteen (3.2%) were known to have died. Thus 92.7% of 497 cases had been traced at five years. Of the remaining 36 untraced cases, 9 were known to be alive at the end of four years, 9 at the end of three years, 8 at the end of two years, 1 at the end of one year, and 9 were lost before the end of the first year.

*This report is being published simultaneously in the *British Medical Journal* in the United Kingdom, in *Circulation* in the United States, and in the *Canadian Medical Association Journal* in Canada.

TABLE I.—*Number of Cases Traced at 5 Years According to Cardiac Groups U.K., U.S., U.K. and U.S.*

Cardiac Group at Start of Treatment	No. of Cases					
	At Start of Treatment	Died	Alive and Heart Status Known	Alive but Heart Status Unknown	Untraced	
					No.	%
U.K.:						
Group A—no or questionable carditis; no pre-existing heart disease	41	0	37	0	4	9·8
Group B—carditis present; no pre-existing heart disease	123	4*	109	4	6	4·9
Group C—with definite or questionable pre-existing heart disease	76	7†	61	3	5	6·6
All groups	240	11	207	7	15	6·2
U.S.:						
Group A—no or questionable carditis; no pre-existing heart disease	76	0	66	4	6	7·9
Group B—carditis present; no pre-existing heart disease	129	1	112	6	10	7·8
Group C—with definite or questionable pre-existing heart disease	52	4	41	2	5	9·6
All groups	257	5	219	12	21	8·2
U.K. and U.S.:						
Group A—no or questionable carditis; no pre-existing heart disease	117	0	103	4	10	8·5
Group B—carditis present; no pre-existing heart disease	252	5*	221	10	16	6·3
Group C—with definite or questionable pre-existing heart disease	128	11†	102	5	10	7·8
All groups	497	16	426	19	36	7·2

* 1 death from acute nephritis and uraemia. † 1 death from acute intestinal obstruction.

The numbers of deaths and the numbers successfully followed up are given in more detail in Table I, where the cases have been divided into three groups according to the status of the heart on admission to the trial—namely, Group A, no or questionable carditis and no pre-existing heart disease; Group B, carditis present but no pre-existing heart disease; and Group C, definite or questionable pre-existing heart disease.†

At the end of five years the fact of death or the status of the heart among the survivors had been recorded in 88% in Group A, 90% in Group B, and 88% in Group C. Similarly, the figures for the three treatment groups were 91% A.C.T.H., 89% cortisone, and 87% aspirin. The corresponding figure was 91% for the U.K. and 87% for the U.S.

It is clear that within these classifications no differential losses, which might obscure comparisons, have taken place.

†The diagnostic criteria for admission to the study specified carditis as shown by any one of the following. (*a*) Development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation. (*b*) Change of heart size of more than 15% on standard *x*-ray film by any standard method of measurement. (*c*) Pericarditis revealed by a definite friction rub or by pericardial effusion. (*d*) Congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnoea, (2) orthopnoea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure, or (6) oedema.

In the assessment of carditis as a criterion for entry to the trial, it was assumed, in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients, observations of changes in heart size and murmurs were used in determining carditis and recorded.

Deaths

Of the 497 children under the age of 16 who were admitted to the study and completed the prescribed course of treatment only 14 had died from rheumatic fever or rheumatic heart disease by the end of the five years of follow-up.‡ One of these deaths occurred shortly after the end of treatment and 4 more within the first year of follow-up. There were no deaths in second year and only one in the third, followed by 4 deaths in the fourth year and 4 in the fifth. In addition, there were 2 deaths from unrelated causes—namely, one in the A.C.T.H. group from acute nephritis and uraemia in the fourth year, and one in the cortisone group from acute intestinal obstruction in the fourth year.

Division by treatment of the 14 deaths due to rheumatic fever or rheumatic heart disease shows 7 among the 162 A.C.T.H. cases (4.3%), 2 among the 167 cortisone cases (1.2%), and 5 among the 168 aspirin cases (3.0%). Division by cardiac status at the start of treatment (Tables I and IX) shows no deaths at all in the 117 Group A cases (cases with no or questionable carditis and without pre-existing heart disease), 4 deaths (1.6%) among the 252 Group B cases (carditis present but no pre-existing heart disease), and 10 (7.8%) among the 128 Group C cases (with pre-existing heart disease). Of the Group B cases, one death occurred among the 37 cases with failure and/or pericarditis at entry (2.7%) and 3 deaths in the remaining 215 cases (1.4%), where these features were absent. Six of the 10 deaths in Group C occurred in a small group of 31 cases where there was already failure and/or pericarditis at the start of treatment. In other words, death occurred in one out of every five of these cases, compared with 1 in 25 in the remainder of Group C.

There were more deaths among females (9 in 238, or 3.8%) than among males (5 in 259, or 1.9%), but the difference might very easily be due to chance. There were also more deaths among those whose disease was six weeks or more in duration when treatment was started than among those treated within six weeks of onset (8 of 104, or 7.7% compared with 6 of 393, or 1.5%). The difference occurred entirely in the Group C cases, where the death rate was 17.5% among late-treated cases as compared with 3.4% in early-treated cases (7 of 40 and 3 of 88 cases). In Group B the rates for late- and early-treated cases were 1.9% and 1.5% respectively (1 of 54 and 3 of 198 cases). The death rate was not significantly lower among those treated within two weeks of onset (3 of 255, or 1.2%) than among those treated at two to six weeks (3 of 138, or 2.2%).

One of the most remarkable features of this study is the very low case fatality in comparison with previous reports.[2-5] In addition to the modern treatment of the disease, there may, however, be a number of other factors concerned in this striking decrease in the severity of the disease. These factors could include a change in the natural history of rheumatic fever or streptococcal infection, the introduction of penicillin and sulphadiazine prophylaxis, and environmental features associated with the higher standard of living.

‡One child given cortisone, who died 20 hours after the start of treatment, is not included in the 497 children or the 14 deaths. With this single exception all the patients survived the course of treatment. The death rates following these courses can therefore be compared without the introduction of any bias due to the incidence of deaths during treatment.

There were also six severely ill patients reported in the U.S. as being kept out of the trial of randomized treatments in addition to the one death after 20 hours of treatment (see preceding footnote). On the other hand, not included in this study are cases of rheumatic fever too mild to be admitted to the study hospitals, a number of which limit their admissions to rheumatic fever and receive referrals from other hospitals. In other words, the case-fatality rate could have been biased in either direction by these selective factors.

Recurrences

The study plan specified that all cases should receive daily prophylaxis with sulphadiazine, after initial eradication of the streptococcus with a 10-day course of penicillin. In spite of this schedule, recurrences did occur, and, for analytical purposes, were defined as the appearance, after an interval of at least three months of freedom from rheumatic activity, of manifestations that would have originally qualified the patient for admission to the trial. An analysis was made of all cases re-treated for such a recurrence. There were, in total, 64 such re-treated recurrences in the five years among 56 different cases of the 497 admitted (11%). In addition, there were 16 re-treated recurrences among 14 cases in which chorea was the only manifestation in the recurrences.

It is more informative, however, to limit attention to the cardiac groups A and B, since many cases in Group C had continuous rheumatic activity, making recurrence impossible to identify. In groups A and B there were, excluding recurrences of pure chorea, 42 recurrences, and 36 cases in which they occurred were divided almost exactly among the three treatment groups. Thus there were 16 recurrences in 12 of the 114 A.C.T.H. cases, 12 recurrences in 12 of the 128 cortisone cases, and 14 recurrences in 12 of the 127 aspirin cases. It is clear that the frequency of re-treated recurrences does not bias the subsequent comparisons of the treatments used in this study.

Comparison of the Treatments

The dosage schedules of A.C.T.H., cortisone, and aspirin were based on published studies and unpublished reports at that time (1950), the aim being to select a dosage likely to be effective over a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs.

The schedules were as follows§:

A.C.T.H.—U.K. cases. A daily dosage in U.S.P. units of 80 for the first four days, 60 for the next three days, 40 for the second and third weeks, 30 for the fourth and fifth weeks, and 20 for the sixth week.

U.S. cases. 120 U.S.P. units for the first four days, 100 for the next three days, 80 for the second week, 60 for the third week, 40 for the fourth and fifth weeks, and 20 for the sixth week.

Cortisone.—A daily dosage of 300 mg. for the first day, 200 mg. for the next four days, 100 mg. for the second and third weeks, 75 mg. for the fourth and fifth weeks, and 50 mg. for the sixth week.

Aspirin.—A daily dosage of 60 mg. per pound of body weight of 10 g. (whichever was less) for the first two days, 40 mg. per pound or 10 g. (whichever was less) for the next five days, and 30 mg. per pound for the second to sixth weeks.

If re-treatment was necessary at any time during the three months following the original course of therapy, then a four-week re-treatment scheme was followed, using the same drug and dosage as in the first four weeks of initial therapy. No patient was re-treated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially. If, after three months without activity, the patient developed a new attack of rheumatic fever, he was treated as in the original course—that is, for six weeks on the same drug and dosage, followed by a three-week period of observation.

The results among cases followed for five years are analysed in terms of the cardiac groups already defined.

Looking first at Group A (Table II), it will be seen that 6 of the 37 A.C.T.H. cases had a murmur at the end of five years (all grade I apical systolic murmurs), 1 of the 33 cortisone-treated cases (a basal diastolic murmur), and 1 of the 33 aspirin-treated group (a grade I apical systolic murmur). The small excess in the A.C.T.H. group is not statistically significant. The striking fact which emerges from this comparison is the exceedingly small proportion of Group A cases treated at these dosage levels of A.C.T.H., cortisone, and aspirin, in which there is evidence of heart disease at the end of five years of follow-up. The prognosis in cases without carditis, but otherwise meeting the criteria for the diagnosis of rheumatic fever, is so good that it would be unreasonable to expect that large-dose cortisone therapy could significantly improve it. The well-recognized occasional severe toxic manifestations in large-dose cortisone therapy also militate against its use in such cases.[6]

In Group B (Table II) the cases are divided into six subgroups according to their cardiac status, ranging from the mildest with only a grade I apical systolic

TABLE II.—*Number of Cases Followed Up for 5 Years and Proportion with One or More Murmurs at that Time, According to Treatment Given and Initial Cardiac Status. U.K. and U.S.*

Cardiac Group at Start of Treatment	A.C.T.H.			Cortisone			Aspirin		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%		No.	%
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	33	1	*3*	33	1	*3*
Group B—carditis present; no pre-existing heart disease:									
(1) Apical systolic murmur grade I, only	5	0	*0*	19	3	*16*	15	4	*27*
(2) Apical systolic murmur grade II or III, only	18	4	*22*	17	7	*41*	25	8	*32*
(3) Apical systolic *and* apical mid-diastolic murmurs	12	9	*75*	15	6	*40*	17	8	*47*
(4) Basal diastolic murmur only	3	2	*67*	5	1	*20*	3	0	*0*
(5) Basal diastolic *and* other murmurs	16	9	*56*	9	4	*44*	9	5	*56*
(6) With failure and/or pericarditis	13	11	*85*	13	8	*62*	7	4	*57*
Group C—with definite or questionable pre-existing heart disease:									
(1) Without failure and/or pericarditis	26	17	*65*	27	21	*78*	27	18	*67*
(2) With failure and/or pericarditis	10	10	*100*	7	7	*100*	5	5	*100*

§Further details of the treatment schedule, including control of auxiliary therapy, can be found in the original report.[1]

murmur‖ to the most severe with pericarditis and/or failure. Examination of these groups shows no consistent difference in favour of any one treatment, but the number of cases in each group is small. Direct comparison of the effects of treatment among the total of cases in Group B is not valid because of the unequal distribution of cases of different degrees of clinical severity among the three treatment groups. For example, there were more severely ill cases in the A.C.T.H. group and more of the milder cases in the cortisone group. There were only 5 A.C.T.H. in comparison with 19 cortisone cases in the group of mild cases with only a grade I apical systolic murmur. On the other hand, there were 16 cases with a basal diastolic and one or more other murmurs in the A.C.T.H. group, compared with only 9 in the cortisone group. Also, there were only 7 cases with pericarditis and/or failure in the aspirin group in comparison with 13 on A.C.T.H. and 13 on cortisone treatment.

It is, however, possible to allow for this unequal distribution of cases of varying degrees of clinical severity among the three treatment groups and thus make a valid evaluation of treatment within the entire Group B. Making the assumption that in each of the cardiac subgroups the three treatments had no differential effects whatsoever, it is possible to calculate the expected outcome in Group B cases for each of the three treatment groups.¶ The expected figures may then be compared with those which actually occurred. Thus, for A.C.T.H. the expected number of cases having murmurs at five years was 31 as compared with 35 observed, for cortisone 31 expected versus 29 observed, and for aspirin 30 expected and 29 observed. There is no evidence in this comparison that the prognosis has been affected more by one treatment than by another.

An alternative analysis of this important Group B can also be made by comparing separately all cases with a single murmur at the start of treatment and those with two or more murmurs at that time (Table III). Among cases with a single murmur at start of treatment, 23% of those on A.C.T.H., 27% on cortisone, and 28% on aspirin still had one or more murmurs at five years—a negligible difference between the treatments. For those who initially had two or more murmurs, the corresponding proportions were 64% A.C.T.H., 42% cortisone, and 50% aspirin. For cases with failure and-or pericarditis at start of treatment the proportions were 85% for A.C.T.H., 62% for cortisone, and 57% for aspirin. In short, in the Group B cases there is no pattern in these results to indicate any advantage for one or another of the forms of treatment.

‖ In this study the following grades were adopted for reporting apical systolic murmurs: *Grade O:* No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border. *Grade P:* Murmur apparently localized to the apical area, but so faint as not to be transmitted to or towards the axilla. The "P" murmurs were not considered indicative of carditis. *Grade I:* Soft apical systolic murmur transmitted to or towards the axilla. *Grade II:* Louder similar murmur. *Grade III:* Very loud similar murmur, usually transmitted to the back.

¶The proportions with murmurs at five years were taken separately for the U.S. and the U.K. for each of six subgroups in Group B *for all three treatments combined*. These proportions were applied to the actual number of patients *on each treatment* and in each of the six subgroups (U.S. and U.K. separately) to see how many in the small subgroups would have had a murmur at five years if they had experienced the total rate of occurrence The "expected" numbers in each small subgroup were then added to give the total number of Group B cases expected to have murmurs. The numbers expected can then be compared with the observed numbers of cases with murmurs at five years.

TABLE III.—*Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed-up for 5 Years and Proportion with One or More Murmurs at that Time. According to Treatment Given and Initial Cardiac Status. U.K. and U.S.*

Cardiac Subgroup at Start of Treatment	A.C.T.H.			Cortisone			Aspirin		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%		No.	%
Group B—carditis present; no pre-existing heart disease:									
(1) One murmur, any grade	26	6	23	41	11	27	43	12	28
(2) Two or more murmurs, any grade	28	18	64	24	10	42	26	13	50
(3) With failure and/or pericarditis	13	11	85	13	8	62	7	4	57

Finally, of the Group C cases without failure and/or pericarditis at the start of treatment (Table II) there were 26 on A.C.T.H., 27 on cortisone, and 27 on aspirin. At five years 17 (65%), 21 (78%), and 18 (67%) respectively had murmurs. Of the 22 Group C cases with failure and/or pericarditis 10 were treated with A.C.T.H., 7 with cortisone, and 5 with aspirin. In every one of these cases murmurs were present at five years. There is once again no evidence of any significant difference between the three treatment groups.

The Evolution of Rheumatic Heart Disease

Since there is no evidence that the treatments varied in their effectiveness, the three groups can be added together for the study of the evolution of rheumatic heart disease in this particular series of patients. The essential division is the cardiac status when treatment was begun.

Cardiac Group A

Of the 103 cases in this group 12 (12%) had a murmur at one year. At five years** (Table IV) the figure is 8, or 8% (7 with grade I apical systolic murmur and 1 with a basal diastolic murmur). It appears that the outlook is better for the 71 cases without any murmur than for the 32 with a questionable murmur†† at the start of treatment—96% with no apparent heart disease compared with 84%. The difference is not formally significant, but it appears in both countries and is in accordance, as shown later, with the general trend of the results.

The number of re-treated recurrences in Group A was 10, but none of the nine cases followed for five years had a murmur at that time.

In summary, the prognosis for the cases without carditis when treatment is started (Group A) is excellent. None of the patients had died, and 92% were without apparent heart disease five years later.

**Murmurs in all cardiac groups both appeared and disappeared in the time interval between one and five years. Thus in some cases murmurs present at one year were absent at five years, while in other cases that were without murmurs at one year a murmur was present at five years.

††The questionable apical systolic murmur (P murmur) was defined differently in the United States than in the United Kingdom. This difference affects the comparison of the results between the countries and the interpretation of the natural history of the disease. In the U.S., each principal investigator was permitted to classify a doubtful apical systolic murmur as a P murmur. In the U.K., however, the Working Party agreed that each investigator make a firm decision as to the presence or absence of an apical systolic murmur at the time of admission of the cases to the study. (A few cases, 7, were called doubtful in the U.K.) In the U.K. some patients with doubtful apical systolic murmurs were unquestionably labelled "no murmur," others were labelled "apical systolic murmur" and included in Group B.

TABLE IV.—*Cardiac Group A (No or Questionable Carditis; No Pre-existing Heart Disease). Number of Cases Followed Up for 5 Years and Proportion with One or More Murmurs at that Time. U.K., U.S., U.K. and U.S.*

Cardiac Subgroup at Start of Treatment	U.K.			U.S.			U.K. and U.S.		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%		No.	%
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	66	2	*3*	103	8	*8*
No murmur ..	30	3	*10*	41	0	*0*	71	3	*4*
Questionable murmur*	7	3	*43*	25	2	*8*	32	5	*16*

* A murmur apparently localized to the apical area but so faint as not to be transmitted to or toward the axilla.

Cardiac Group B

Of the 252 cases in this category originally admitted to the study 5 had died, 10 were known to be alive although their cardiac status was unknown, and the cardiac status at five years had been recorded for 221.

The remaining 16 had been lost (Table I). As has already been shown, the group is clinically heterogeneous and for analysis of the five-year results has been subdivided in Table V into five subgroups of murmurs (without failure and/or pericarditis) and one subgroup comprising cases with failure and/or pericarditis. The untraced cases were spread evenly over these subgroups. Confining attention first of all to the total figures (U.K. and U.S.), the following results may be noted:

(1) *Cases with a Grade I Apical Systolic Murmur Alone.*—Of the 39 cases with only a grade I apical systolic murmur at the start of treatment 14, or 36%, had murmurs at one year, while at five years the number had fallen to 7, or 18% (3 with a grade I apical systolic murmur, 1 with a grade III apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic, apical systolic, and mid-diastolic murmurs, and 1 with apical systolic and pre-systolic murmurs). Thus 82% of this group had no apparent heart disease at five years and none had died.

(2) *Cases with a Grade II or III Apical Systolic Murmur Alone.*—Of the 60 cases in this category 32, or 53%, had at least one cardiac murmur at one year. This figure had decreased considerably at five years to 19, or 32% (6 with grade I apical systolic murmurs, 5 with grade II or III apical systolic murmurs, 5 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic and apical systolic murmurs, and 2 with known but unspecified murmurs). Thus among these cases 68% had no apparent heart disease at five years. Two additional cases originally in this group had died, both in the first year.

(3) *Cases with an Apical Systolic Murmur of any Grade Plus an Apical Mid-diastolic Murmur.*—Of the 44 cases in this category 28, or 64%, had at least one murmur at one year, while at five years the number was 23, or 52% (6 with an apical systolic murmur grade I, 6 with an apical systolic murmur grade II or III, 4 with an apical systolic and an apical mid-diastolic murmur, 2 with a basal diastolic murmur and an apical systolic murmur, and 3 with a basal diastolic murmur an apical systolic and a mid-diastolic murmur, and finally, 2 with an apical pre-systolic murmur accompanied by an apical systolic murmur in the first and by an apical systolic and a basal diastolic murmur in the second). Thus among these cases only about half (48%) had no apparent heart disease at five years. In addition, one had died during the fourth year but not from rheumatic fever.

(4) *Cases with a Basal Diastolic Murmur Alone.*—There were only 11 cases in this category, of whom 5, or 45%, had at least one murmur at one year, decreasing to 3 cases, or 27%, at five years (2 with basal diastolic murmurs alone, 1 with unspecified murmurs). Thus 73% of this group had no apparent heart disease at five years. None had died.

(5) *Cases with a Basal Diastolic Murmur and an Apical Systolic and/or a Mid-diastolic Murmur.*—Of the 34 cases in this category at five years, 33 were reported at one year, and of these, 22, or 67%, had at least one murmur at that time. The figure decreased to 18 out of 34 cases or 53% at five years (4 with a grade II apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with an apical mid-diastolic murmur alone, 7 with a basal diastolic murmur alone, and 5 with a basal diastolic murmur and another murmur, 4 of which were apical systolic and 1 a mid-diastolic murmur). Thus almost one-half of this group (47%) had no apparent heart disease at five years. In addition, one patient had died during the fifth year.

(6) *Cases with Failure and/or Pericarditis.*—Turning finally to the cases in Group B with failure and/or pericarditis at the start of treatment, there were 33 such cases, of which 24, or 73%, had at least one murmur at one year. At five years 23, or 70%, had a murmur (4 with a grade I apical systolic murmur, 8 with a grade II or grade III apical systolic murmur, 3 with apical systolic and mid-diastolic murmurs, 2 with a basal diastolic murmur alone, and 6 with a basal diastolic murmur and other murmurs, of which 3 were apical systolic, 2 were apical systolic and mid-diastolic, and 1 was apical pre-systolic and mid-diastolic). In other words, only 30% of this group were without apparent heart disease at five years. In addition, one patient had died during the fourth year.

TABLE V.—*Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed Up for 5 Years and Proportion with One or More Murmurs at that Time. U.K., U.S., U.K. and U.S.*

Cardiac Subgroup at Start of Treatment	U.K.			U.S.			U.K. and U.S.		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%		No.	%
Without failure and/or pericarditis ..	97	36	*37*	91	34	*37*	188	70	*37*
(1) Apical systolic murmur grade I, only	14	4	*29*	25	3	*12*	39	7	*18*
(2) Apical systolic murmur grade II or III, only	28	10	*36*	32	9	*28*	60	19	*32*
(3) Apical systolic *and* apical mid-diastolic murmurs ..	24	11	*46*	20	12	*60*	44	23	*52*
(4) Basal diastolic murmur only	6	1	*17*	5	2	*40*	11	3	*27*
(5) Basal diastolic *and* other murmurs	25	10	*40*	9	8	*89*	34	18	*53*
With failure and/or pericarditis ..	12	10	*83*	21	13	*62*	33	23	*70*

Comparison of the U.K. and U.S. experiences in all Group B cases (Table V) reveals no consistent pattern of advantage or disadvantage. The largest difference, which lies in the group with basal diastolic plus other murmurs, is almost entirely a function of a differing standard of interpretation, since the U.K. figure is derived from one centre only. Thirty of the total 31 U.K. cases with a basal diastolic murmur at start of treatment whose status was known at five years were reported from this centre. The basal diastolic murmurs in cases at this centre were soft, and 25 of the 30 disappeared.

An analysis was made of other factors which might have prognostic effects. These included sex, age, duration from onset, and presence or absence at start of treatment of polyarthritis, nodules, chorea, and prolonged P–R interval. None of these individually appeared to affect the evolution of rheumatic heart disease as measured by the presence of murmurs at five

years (Table VI). Cardiac enlargement as measured by a cardiothoracic ratio on the teleoroentgenogram of 0.60 or greater was present at start of therapy in 16 Group B cases. In 13 of these at least one murmur was present at five years. This serious prognosis is explained by the large number of such cases (11 of 16) that had cardiac failure and/or pericarditis at start of treatment, practically all of which (10 of 11) had at least one murmur at five years.

TABLE VI.—*Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases Followed Up for 5 Years and Numbers Expected* and Observed to Have Murmurs at 5 Years According to Sex, Age, Duration from Onset, and Presence or Absence of Various Signs or Symptoms. U.K. and U.S*

Status at Start of Treatment	No. of Cases	No. with Murmurs at 5 Years	
		Observed	Expected*
Males	104	41	44
Females	117	52	49
Under 10 years of age	119	55	54
10-16 " " "	102	38	39
0-14 days from onset	102	38	39
15+ " " "	119	55	54
P-R 0·18+	54	15	20
P-R <0·18	167	78	73
With joint involvement	76	26	30
Without " "	145	67	63
With nodules	38	20	17
Without "	183	73	76
With chorea	30	8	11
Without "	191	85	82

* Expected numbers take account of differences in the severity of cardiac involvement among the groups being compared. They were calculated in the following manner: The proportions of cases with murmurs at five years were taken separately for the U.S. and the U.K. for each of the six cardiac subgroups in Group B. These proportions were applied in the U.S. and U.K. separately to the actual number of patients in each cardiac subgroup of the categories listed above to see how many in the small subgroups would have had a murmur at five years if they had experienced the total rate of occurrence. The "expected" numbers in the subgroups were added to get the total number expected in each category for the U.S. and U.K. combined.

TABLE VII.—*Cardiac Group B (Carditis Present; No Pre-existing Heart Disease). Number of Cases With and Without Retreated Recurrences and Proportion with One or More Murmurs at 5 Years. U.K. and U.S.*

Cardiac Subgroup at Start of Treatment	Without Re-treated Recurrences			With Re-treated Recurrences		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%
Group B—carditis present; no pre-existing heart disease:						
(1) One murmur, any grade	102	26	*25*	8	3	*38*
(2) Two or more murmurs, any grade	69	32	*46*	9	9	*100*
(3) With failure and or pericarditis	25	16	*64*	8*	7	*88*

* Excludes one case with re-treated recurrence which was not traced at 5 years.

Re-treated recurrences occurred in 25 Group B cases whose cardiac status at start of treatment was, on the average, more severe than in the remainder of Group B cases (Table VII). At five years these re-treated patients had a larger proportion with murmurs than those without re-treated recurrences. However, the relationship between cardiac status at start of therapy and at five years still held even though re-treated attacks had occurred in the interim. Among Group A cases there were no murmurs at five years in 9 cases with re-treated recurrences; in Group B cases with a single murmur at start of treatment 3 out of 8 cases had murmurs at five years as compared with 9 out of 9 in cases with two or more murmurs and 7 out of 8 cases with failure and/or pericarditis.

Summarizing the cases with carditis but without pre-existing heart disease (Group B), it is clear that prognosis is directly dependent on the amount and severity of cardiac involvement at the start of treatment, the proportion with a murmur at five years varying from 18% in those with a grade I apical systolic murmur to 70% among those with pericarditis and/or failure. Excluding the group with basal diastolic murmurs for the reason given above, and because of the relatively few cases in this category in the U.S., this trend holds when the figures are examined individually for each country. In addition, the proportion of all Group B cases with murmurs is remarkably similar in the two countries.

Cardiac Group C

There were 102 patients with known cardiac status at five years who had definite or questionable pre-existing heart disease at the start of their treatment (Table VIII).

TABLE VIII.—*Cardiac Group C (Definite or Questionable Pre-existing Heart Disease). Number of Cases Followed Up for 5 Years and Proportion with One or More Murmurs at that Time. U.K., U.S., U.K. and U.S.*

Cardiac Subgroup at Start of Treatment	U.K.			U.S.			U.K. and U.S.		
	No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years		No. of Cases	With Murmurs at 5 Years	
		No.	%		No.	%		No.	%
Without failure and/or pericarditis	45	36	*80*	35	20	*57*	80	56	*70*
With failure and/or pericarditis	16	16	*100*	6	6	*100*	22	22	*100*

Of the 80 without failure and/or pericarditis at that time, 70% had heart disease at five years, and of the 22 with failure and/or pericarditis, all had heart disease. It may also be recalled that in addition four and six deaths from rheumatic fever had taken place respectively in these two groups and one death from other causes in the group without failure or pericarditis.

Prognosis in Relation to Cardiac Status

In Table IX all of the cases in the study followed for five years are listed in the order of increasing severity of heart disease at start of treatment. It is abundantly clear that the range from 96% to 0% with normal hearts at five years is much more striking than differences reported here or ascribed elsewhere to the effects of treatment. Thus in the prevention of rheumatic heart disease no evaluation of therapy of acute rheumatic fever can be valid unless this major

TABLE IX.—*Prognosis in Relation to Cardiac Status at Start of Treatment. U.K. and U.S.*

Cardiac Status at Start of Treatment	No. of Cases Observed for 5 Years	Per cent. with No Murmur at 5 Years	No. of Deaths in 5 Years
Group A:			
No carditis	71	*96*	0
Questionable carditis	32	*84*	0
Group B:			
Apical systolic murmur grade I, only	39	*82*	0
Apical systolic murmur grade II or III, only	60	*68*	2
Apical systolic *and* apical mid-diastolic murmurs	44	*48*	1†
Basal diastolic with or without other murmurs	45 (15)*	*53 (27)**	1
Failure and/or pericarditis	33	*30*	1
Group C:			
Pre-existing heart disease without failure and/or pericarditis	80	*30*	5‡
Pre-existing heart disease with failure and/or pericarditis	22	*0*	6

*Excluding one U.K. centre.
†Death from acute nephritis and uraemia.
‡Includes one death from acute intestinal obstruction.

factor is taken into account in the design of the study or the analysis of the data. This conclusion is reinforced by the occurrence of most of the deaths from rheumatic fever (10 of 14) among cases with pre-existing heart disease, and the absence of deaths among the cases without heart involvement at start of treatment.

No comparisons have been made with the conflicting reports of results obtained with large-dose hormone therapy,[7-11] the most recent of which shows no advantage in a well-controlled study.[11] A firm decision on the efficacy of large-dose hormone treatment of rheumatic fever will depend on controlled studies of adequate size in which the initial status of the heart is taken into account.

Summary

A study has been made at the end of five years after the conclusion of treatment of the 497 children who were admitted to the U.K./U.S. co-operative clinical trial of the relative merits of A.C.T.H., cortisone, and aspirin in the treatment of acute rheumatic fever.

Four hundred and forty-five of the cases (89.5%) were followed for the complete five years, and the status of the heart was known for 426 of them. Only 16 (3.2%) had died, 14 of them from rheumatic heart disease; 36 (7.2%) were untraced. The very low fatality rate is striking.

At the end of five years there is no evidence, on the treatment schedule used in this study, that the prognosis has been influenced more by one treatment than another. This confirms the findings reported at one year.

The major factor in determining the incidence of rheumatic heart disease at the end of five years is the status of the heart at the time treatment was begun. For cases without carditis initially the prognosis was excellent, since in 96% there was no residual heart disease. In cases with carditis initially, but without pre-existing heart disease, the proportion without residual heart disease decreased progressively from 82% for those with only a grade 1 apical systolic murmur to 30% for those with failure and/or pericarditis. In cases with pre-existing heart disease the prognosis was poor. Only 30% of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at five years.

Cases with carditis and without pre-existing heart disease which had recurrences demanding retreatment during the follow-up period had on the average a more severe cardiac status at start of treatment than did those without recurrences requiring re-treatment. At five years a larger proportion of these re-treated cases had murmurs.

These results make it clear that treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is taken closely into account.

The National Heart Institute of the United States Public Health Service supported the study with grants to the co-ordinating centre and to the co-operating centres in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centres and for a co-ordinating registrar in the United Kingdom. The centre in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States the costs of the medical care of its patients were met by each co-operating centre, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Co-ordinating Centre and a grant for statistical services.

This co-operative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck and Company, and space and services by the Helen Hay Whitney Foundation.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

REFERENCES

1 Joint Report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-committee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, *Circulation*, 1955, **11**, 343; *Brit. med. J.*, 1955, **1**, 555.
2 Findlay, L., *The Rheumatic Infection in Childhood*, 1931, chap. 12. Arnold, London.
3 Ash, R., *Amer. Heart J.*, 1948, **36**, 89.
4 Wilson, M. G., and Lubschez, R., *J. Amer. med. Ass.*, 1948, **138**, 794.
5 Bland, E. F., and Jones, T. D., *Circulation*, 1951, **4**, 836.
6 Good, R. A., Vernier, R. L., and Smith, R. T., *Pediatrics*, 1957, **19**, 95, 272.
7 Greenman, L., Weigand, F. A., and Danowski, T. S., *Ann. rheum. Dis.*, 1953, **12**, 342.
8 Markowitz, M., and Kuttner, A. G., *Pediatrics*, 1955, **16**, 325.
9 Roy, S. B., and Massell, B. F., *Circulation*, 1956, **14**, 44.
10 Ferencz, C., Markowitz, M., and Bunim, J. J., *A.M.A. J. Dis. Child.*, 1959, **97**, 561.
11 Combined Rheumatic Fever Study Group, *New Engl. J. Med.*, 1960, **262**, 895.

DISINFECTION OF THE SKIN OF OPERATION SITES

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Disinfection of the skin has been assessed in terms of the removal of superficial organisms only or of organisms from the deeper as well as the more superficial layers. Gardner and Seddon (1946), Gardner (1948), and Story (1952) found that several antiseptics (notably 1% iodine in alcohol) could, in 20 to 30 seconds, bring about "virtual disinfection"—that is, removal of 99.9% or more—of organisms previously deposited and allowed to dry on the skin; in their view the dangers of wound infection come largely from the superficial or "transient" flora which they simulated in their tests. Price (1938, 1957) described a method of serial hand-washing by means of which estimates of the deeper (or "resident") flora could be made; by this method considerable numbers of resident organisms were found to persist after two minutes' exposure to various antiseptics, including 1% iodine in alcohol. Most of the deeper bacteria proved to be harmless commensals, but pathogenic organisms were also found among them.

The surgeon's knife will carry surviving bacteria from all levels of the skin to the tissues, so it is desirable to know the effects of antiseptics on the bacteria of the deeper layers as well as on the transient bacteria of the

surface. Moreover, as the deeper bacteria are not completely removed even by the most effective antiseptic, it is possible to make quantitative comparisons of the relative effectiveness against them of different antiseptic applications; this cannot be done satisfactorily in tests on the superficial flora.

In the studies reported here we have tested a number of antiseptics both against pathogens deposited on the surface and against the normal skin flora; in the latter study a hand-washing method of sampling was used, and the comparative value of the antiseptics was statistically assessed by the use of a Latin square design. This study included a quantitative comparison of selected modern antiseptics with alcohol and iodine, an assessment of the value of repeated disinfection, and tests of the degree of association between counts of total organisms and of *Staphylococcus aureus* in handwash-sampling before and after disinfection.

Materials and Methods

Antiseptics Tested.—The following antiseptics were tested: ethyl alcohol (70% w/v in water); 1% iodine in 70% ethyl alcohol; 1% iodine with potassium iodide in water (Lugol's iodine); "virac," an iodophore consisting of a quaternary ammonium compound coupled with 0.2% available iodine (Frisch, Davies, and Krippaehne, 1958); 0.5% chlorhexidine ("hibitane") digluconate in 70% ethyl alcohol; 0.5% chlorhexidine diacetate in water; 0.1% phenylmercuric dinaphthyl methane disulphonate ("penotrane") in water; and cetrimide (1% and 2%) in water. Hexachlorophane soaps, which reduce the skin flora on repeated application (see Lowbury and Lilly, 1960), were not included in this study, because their action is slow and therefore less appropriate for operation sites than for the hands of surgeons and nurses.

Tests on Transient Flora

Tests were made on members of the laboratory staff by a method based on that of Story (1952). Three circular areas 4 cm. in diameter were marked out on the front of each forearm. One drop (0.02 ml.) of a washed suspension in Ringer's solution of an overnight nutrient broth culture of a penicillin-resistant *Staph. aureus* was spread in each of these areas. When dry, four of the sites were treated with antiseptic, three drops of which were spread with a wire loop over the whole area and allowed to dry; one or, more often, two control areas were left untreated. Aqueous solutions dried in about two minutes. Alcohol and alcoholic solutions, which dried in about 20 seconds, were tested in this way, and also after repeated applications, to keep the surface moist for about two minutes. Virac, which is a viscous fluid, dried very slowly, and the surface treated with this material was therefore gently blotted dry after two minutes; because of the difficulty of spreading virac, tests were done with six drops as well as three drops applied to the test area.

Bacterial sampling was done by firmly applying truncated glass cylinders, 4 cm. across and about 2.5 cm. deep, to the test areas, measuring 5-ml. amounts of Ringer's solution with neutralizers (see below) into these "cups," and rubbing the skin in a standard way with a glass spreader for 15 seconds. In the tests on the controls, and on all the antiseptics except penotrane, pour-plates were prepared with 1 ml. of tenfold dilutions of the washings in nutrient agar containing the appropriate neutralizers and 0.3 unit of penicillin per ml. to inhibit the growth of normal skin flora. Colonies were counted after 48 hours' aerobic incubation at 37° C. Some tests (on alcoholic iodine and chlorhexidine) were also made with a strain of *Pseudomonas pyocyanea* (1/100 dilution of overnight broth culture) as the test organism.

The following neutralizers were included in the culture medium: for iodine, sodium thiosulphate, 0.04%; for chlorhexidine, "lubrol W" 1% and lecithin 0.5%; for virac, sodium thiosulphate 1% and "tween 80," 1%; for cetrimide, sterile milk (an equal volume added to the washings before pouring plates); for penotrane, sodium thioglycollate 0.15% (the highest concentration which was not itself inhibitory to the staphylococcus). To confirm the effectiveness of neutralization, samples were taken as described above from control areas of skin which had been treated with antiseptics, and small inocula (0.02 ml. of 1/500,000 dilution) of broth cultures of *Staph. aureus* were seeded in duplicate, (1) in the sampling fluids and media, and (2) in control fluid and medium. Viable counts showed that neutralization was complete for all the antiseptics except cetrimide and penotrane.

For penotrane, which appeared in preliminary tests to have destroyed the staphylococci deposited on the skin, we adopted a modified sampling method in which 1-ml. washings were diluted (1/10) and divided between the smallest number of pour-plates (about 20) which showed no inhibition of added staphylococci.

Tests on Resident Flora

The method of sampling was similar to one previously used for the assessment of hexachlorophane soap (Lowbury and Lilly, 1960). The hands were first washed with ordinary bar soap and water under a running tap for 30 seconds, and dried on a sterile towel. A sample of hand-washings was then taken in 100 ml. of a sampling fluid in a bowl (Ringer's solution with a mixture of neutralizers described below). Both hands were thoroughly moistened and then rubbed firmly three times palm to palm, three times with the right palm over the left dorsum, three times with the left palm over the right dorsum, and three times with fingers interlacing; the hands were thoroughly rinsed before and after each of these procedures, and an effort was made to keep the technique as consistent as possible.

After this sampling the hands were rinsed in running water and dried on a sterile towel, and the antiseptic was applied with a gauze swab to the whole surface of both hands, the skin being kept visibly moist for approximately two minutes; to achieve this a single application of aqueous solutions and one or two reapplications of alcoholic solutions were required; virac was blotted dry after two minutes. A second sample of hand-washings was then taken by the same method as initially. In the control experiments two successive samplings were made, with a rinse only between the samplings. Tenfold dilutions of the washings were made in sampling fluid, and pour-plates were prepared from 1-ml. amounts of each dilution. After 48 hours' aerobic incubation at 37° C. colonies were counted.

The sampling fluid was Ringer's solution containing sodium thiosulphate (1%), lubrol W (1%), lecithin (0.5%), and tween 80 (1%); the same neutralizers were included in the nutrient agar used for pour-plates. In

this way all the antiseptics which were studied by this method were completely neutralized in the inocula used for counting, as shown by duplicate test inoculation of staphylococci on to the plates used for sampling and on to control plates. In each experiment tests were made by this method for inhibitory traces of antiseptic in the sample plates used for counting.

Since only one treatment can be satisfactorily tested at a time, and since personal variation might be important, a Latin square design was used which permitted the separate calculation of the contributions of effect of treatment, person, and days (Fisher, 1942).

Results

Tests on Transient Skin Flora

The effects of antiseptics on the cultures of *Staph. aureus* deposited on the skin are summarized in Table I.

TABLE I.—*Survival of Added Staph. aureus After Treatment of Skin with Different Antiseptics*

Antiseptic	Approx. Duration of Treatment (min.)	Tests	Viable Counts per ml. Washings from Untreated Areas (Range)	% Organisms Surviving after Treatment†
Ethyl alcohol (70%)	0·4*	4	39,520–122,000	0·008–1·2
	2·0	3	236,000	<0·0004
Iodine (1%) in alcohol (70%)	0·4*	7	1,260–7,860	<0·012–0·24
Chlorhexidine (0·5%) in alcohol (70%)	0·4*	2	122,000	0·002–0·03
Lugol's iodine ..	2·0	2	282,000	<0·0003
Virac 3 drops) ..	2·0	2	282,000	<0·0003–0·007
,, (6 ,,)	2·0	2	282,000	<0·0003
Chlorhexidine (0·5%) in water	2·0	2	282,000	<0·0003
Cetrimide (2%) in water	2·0	2	209,000	>0·09–>0·14
Penotrane (0·1%) in water	2·0	4	1,600–81,000	6·4–12·2

* Until evaporation of the fluid.
† Viable counts from treated areas expressed as percentage of viable counts from untreated areas.

No bacteria were isolated from samples taken after two minutes' treatment with 70% ethyl alcohol, with virac, with aqueous chlorhexidine, and with aqueous iodine (Lugol's); after 20 seconds' treatment—that is, until drying—with alcohol and with alcoholic iodine or chlorhexidine, very small numbers of staphylococci were still present, the proportion of survivors being slightly higher with alcohol than with the alcoholic solutions. A much larger proportion of survivors was found after two minutes' treatment with penotrane. Some survivors were found after two minutes' treatment with 1% and 2% aqueous cetrimide, and the effect of this antiseptic was clearly smaller than these tests would suggest, for the milk which was used as a neutralizer did not, in fact, prevent some inhibition by cetrimide transferred to the culture plates.

Quantitative measures of the relative value of different skin antiseptics could not be obtained by this method, and we used it as a screening method for the exclusion of less effective antiseptics. Penotrane and aqueous cetrimide were clearly less effective than the other antiseptics in our series; they were therefore excluded from the next stage of this study—the comparative assessment of antiseptics on the resident skin flora.

Tests on Resident Skin Flora

A comparative study was made on the following antiseptics: 70% ethyl alcohol, 1% iodine in 70% ethyl alcohol, 0.5% chlorhexidine digluconate in 70% alcohol, Lugol's iodine, 0.5% chlorhexidine diacetate in water, and virac. Each of these agents, and a control rinse in running water, were tested on the hands of each of seven subjects; a minimum of one week was left between tests. Since the treatments were randomly allotted in a Latin square design, each treatment had equal chances of being affected by possible variation due to differences such as room temperature or humidity on different days. The performance of each agent was measured by the reduction in bacterial counts after its use, expressed as a percentage of the initial counts. Table II shows these results and averages derived from them. Analysis of variance (Table III) demonstrates a marginally significant variance due to differences

TABLE III.—*Analysis of Variance*

Item	Sum of Squares	Degrees of Freedom	Mean Square	Significance
"Persons"	378	6	63	Not sigt. (p>0·2)
"Days" ..	2,164	6	361	Borderline p=0·05
"Treatment" ..	21,318	6	3,553	Sigt., p<0·001
Residual	4,823	30	160·7	—
Residual+"Persons" ="Error" ..	5,201	36	145	(S.D. of single observation=12)

TABLE II.—*Reduction in Bacterial Counts from Hand-washings expressed as Percentage of Initial Count (Measured at 10^{-2} Dilution)*

	Days							Totals (Treatments)	Mean % Reduction
	1	2	3	4	5	6	7		
Alcohol	(5) 72	(1) 53	(6) 59	(3) 60	(4) 67	(7) 93	(2) 76	480	68·6
Alcoholic iodine	(2) 72	(5) 83	(3) 93	(7) 78	(1) 81	(4) 83	(6) 75	565	80·7
Lugol's ,, ...	(6) 67	(2) 73	(7) 35	(4) 76	(5) 70	(1) 89	(3) 62	472	67·4
Alcoholic chlorhexidine ..	(3) 81	(6) 84	(4) 70	(1) 82	(2) 80	(5) 93	(7) 79	569	81·3
Aqueous ,, ..	(7) 60	(3) 79	(1) 64	(5) 35	(6) 76	(2) 66	(4) 45	425	60·7
Virac	(4) 57	(7) 70	(5) 55	(2) 64	(3) 67	(6) 66	(1) 29	408	58·3
Control	(1) −4	(4) 46	(2) 12	(6) 12	(7) 9	(3) 16	(5) 12	103	14·7
Total (days)	405	488	388	407	450	506	378		
Total (persons)	(1) 394	(2) 443	(3) 458	(4) 444	(5) 420	(6) 439	(7) 424		

Numbers in parentheses indicate experimental subjects.

between days. These differences bear no obvious relationship to temperature or humidity, nor to mean initial counts. The method of analysis excludes this variation from the estimate of error. No significant difference of effectiveness was found between persons.* Pooling the variance attributable to persons with the residual, the derived standard error can be used for comparisons between treatments. Two antiseptics—alcoholic chlorhexidine and alcoholic iodine—were clearly better than the rest, with no significant difference between them. Alcohol, Lugol's iodine, aqueous chlorhexidine, and virac were effective in this order, but on the data of this experiment the differences between any pair are not significant. All are less effective than alcoholic iodine or alcoholic chlorhexidine and significantly more effective than the control rinse in running water.

Effect of Penotrane on the Resident Flora

It has been reported that penotrane applied to the surface will penetrate through all the layers of the skin (Goldberg, Shapero, and Wilder, 1950). Although in our tests (see above) its bactericidal effect on superficial organisms was rather poor, it seemed possible that penotrane might have more effect against the deeper flora than other antiseptics which are more active against bacteria deposited on the surface. We therefore tested its disinfectant action on the resident flora by the method described above, modified as follows: (1) the sampling fluid and the culture medium used for pour-plates contained 0.15% sodium thioglycollate as a neutralizer; (2) the sample of hand-washings taken after the treatment with penotrane was diluted 1 in 1,000 in Ringer's solution, and the diluted sample was distributed in 0.1-ml. amounts in 15 to 20 pour-plates, this degree of dilution having previously been found the lowest which did not allow the transfer of bacteriostatic levels of penotrane to the culture plates. Viable counts were made after 48 hours' incubation.

Results.—The reduction in bacteria on the skin after treatment with penotrane (expressed as percentage of the pre-treatment counts) was 28% in the first and 37.7% in the second experiment. This effect was smaller than the reduction in count obtained from any of the antiseptics included in the comparative study reported above (see Table II). In its high bacteriostatic and relatively low bactericidal action penotrane is typical of the mercurial group of antiseptics.

Table IV.—*Effects of Repeated Disinfection with 70% Ethyl Alcohol (2 Minutes) on Six Subjects*

Experiment	Reduction in Bacterial Counts from Hand-washings expressed as % Initial Count after		
	1st Treatment	2nd Treatment	3rd Treatment
1	34	90·7	88
2	63	94·6	92·4
3	77	69	70
4	82	87	90
5	57	68	81
6	74	90	91

Effect of Repeated Antiseptic Treatment of the Skin

The possibility of improving on a single antiseptic treatment by repeating it once or twice, or by doubling or trebling the time of treatment, was tested with 70% ethyl alcohol. After a 30-seconds wash with soap and water the skin was sampled as above for resident organisms. Alcohol treatment for two minutes was followed by another sampling. This was followed immediately by a second and a third two minutes' treatment with alcohol, after each of which the resident organisms were sampled. Six experiments were made, each on a different subject.

Results.—In all but one of these experiments (see Table IV) the reduction in bacterial counts was greater after the first treatment than after the second or third treatment, and in all but one (which showed a marginal effect) there was no further reduction in bacterial count after two periods of treatment; in two of the experiments the counts after two and after three periods of treatment were as high as they were after a single treatment of two minutes.

Effect of Skin Disinfection on Total Organisms and on Staph. aureus

To find whether our hand-washing technique gave some indication of the effect of antiseptic treatment on skin-borne *Staph. aureus*, we made the following tests on eight nurses in the burns unit of this hospital. The nurses were asked to wash their hands with soap and water for 30 seconds. The hands were then dried on a sterile towel, sampled by the hand-washing technique described above, treated with 70% alcohol for one minute, and then sampled again. Tenfold dilutions of the first and second washings were spread on the surface of phenolphthalein diphosphate agar plates (Barber and Kuper, 1951). Total and presumptive *Staph. aureus* counts (the latter after inversion over ammonia) were made after 48 hours' incubation of the plates.

Results.—Table V shows the estimated proportion of total organisms and of *Staph. aureus* persisting after skin treatment with alcohol in the seven nurses from whom staphylococci were isolated. Of these, two nurses showed very small numbers of *Staph. aureus*, and two showed a more complete removal of staphylococci than of total organisms from the hands; in three nurses the proportions of staphylococci and of total organisms removed by the antiseptic were of the same order. We inferred from this observation that staphylococci were represented among the deeper as well as the superficial flora of the skin in more than half of the subjects investigated.

Table V.—*Counts of Bacteria on Nurses' Hands Before and After Disinfection with 70% Alcohol (1 Minute)*

Subject	Totals (per 0·5 ml. Washings)		*Staph. aureus* (per 0·5 ml. Washings)	
	Before	After	Before	After
1	375	275	4	0
2	1,875	700	38	14
3	850	212	27	1
4	2,387	1,000	8	0
5	1,112	762	34	2
6	3,200	2,237	287	187
7	4,712	275	1,087	112

Evidence that Sampling Technique Showed Effect of Antiseptics on Resident Flora

The method which we used for sampling the deeper flora was less arduous than that of Price (1938), who scrubbed the skin with brush and soap in a series of bowls of sampling fluids. For the following reasons, however, it seemed that our method was giving us a fair sample of the resident flora: (1) the percentage

*One subject (No. 3) had to drop out of the trial after two experiments owing to illness. His place was taken by a new volunteer, who continued to the end of the series. Scrutiny of the results reveals no appreciable disturbance due to this change and suggests that it has not seriously impaired the reliability of the trial.

reduction in bacterial flora after treatment with 70% alcohol and with iodine in alcohol was no greater in our experiments than it was in those reported by Price (1957); (2) the percentage reduction in the counts of bacteria deposited on the skin and then exposed to antiseptics was much greater; (3) the removal of staphylococci was more complete than that of the total organisms after the treatment of the hands of two out of seven nurses with 70% ethyl alcohol. This was consistent with the view that in these nurses most of the staphylococci were superficial, and the total flora included representatives of the deeper layers.

The organisms which were sampled after three successive treatments with alcohol appear to have come from a still deeper layer, where they were completely protected from the antiseptic, for their numbers were as great as those present in the samples taken after two such treatments.

Effect of Alcoholic Chlorhexidine and Alcoholic Iodine on Ps. pyocyanea

The experiment reported above (Table III) showed that alcoholic chlorhexidine (0.5%) was as effective as alcoholic iodine (1%) in disinfectant action against the resident flora of the skin. As chlorhexidine is less active *in vitro* against Gram-negative bacilli, and especially against pseudomonas, than against the Gram-positive cocci, we compared the effect of alcoholic iodine and of alcoholic chlorhexidine against *Ps. pyocyanea* deposited on areas of skin, using the method described above for transient flora, but with the suspension of *Ps. pyocyanea* diluted 1 in 100, as recommended by Story (1952); tests were made with a single application of the antiseptic, which dried in about 20 seconds, and with repeated applications to keep the contaminated surface moist for two minutes.

Results.—These are summarized in Table VI. No *Ps. pyocyanea* could be detected after two minutes' treatment with alcoholic iodine or alcoholic chlorhexidine, or after 20 seconds' treatment with alcoholic chlorhexidine; in both experiments with alcoholic iodine some *Ps. pyocyanea* survived 20 seconds' exposure to the antiseptic.

TABLE VI.—*Survival of Added Ps. pyocyanea After Treatment of Skin with Alcoholic Iodide* (1%) *and Alcoholic Chlorhexidine* (0.5%)

Antiseptic	Duration of Treatment	Tests	Viable Counts per ml. Washings from Untreated Areas	% Organisms Surviving after Treatment*
Alcoholic iodine (1%)	2 minutes	3	24,000	<0·004
	20 seconds	2		0·05–10·8
Alcoholic chlorhexidine (0·5%)	2 minutes	3	36,800	<0·0027
	20 seconds	2		<0·0027

* Viable counts from treated areas expressed as percentage of viable counts from untreated areas.

Discussion

Of the two methods of bacteriological sampling used in this study, one gave information about the most superficial organisms of the skin, and these could be virtually eliminated by several alternative methods of disinfection; the other method included in its sample some of the deeper organisms, and the best forms of skin disinfection reduced the skin flora estimated in this way only by about 80%. In disinfection of the surgeon's or the nurse's hands the important object is to prevent the transfer of bacteria from these surfaces to the patients, for which purpose the removal of superficial flora is presumably of first importance. Gardner and Seddon (1946) consider the removal of superficial organisms to be the main concern of disinfection at operation sites, too, because, in their opinion, pathogenic organisms, including *Staph. aureus*, are generally transient. In the majority of our tests on nurses' hands, staphylococci were removed from the skin in approximately the same proportion as the total organisms, from which we inferred that they were present in the deeper as well as the superficial layers. No antiseptic can be claimed to achieve "virtual disinfection" against organisms at this level, and tests with indicator organisms deposited on the skin exaggerate the value of antiseptics by disregarding the deeper flora.

Iodine in alcohol appeared, from the work of Gardner and Seddon (1946) and of Price (1957), to be the most effective skin antiseptic available at the time, but sensitivity of some patients to iodine has caused many surgeons to avoid using it. In our tests, 1% iodine in alcohol and 0.5% chlorhexidine in alcohol showed approximately the same effectiveness in reducing the resident flora, and chlorhexidine does not appear to cause sensitization (Calman and Murray, 1956); ethyl alcohol (70%), Lugol's iodine, virac, and aqueous chlorhexidine (0.5%) were significantly less effective. All of these antiseptics, however, were shown to be highly effective in removing superficial or "transient" staphylococci from the skin, and alcoholic chlorhexidine was at least as effective as alcoholic iodine in removing strains of *Ps. pyocyanea*. In their activity against surface organisms, 1% and 2% aqueous cetrimide and 0.1% aqueous penotrane (especially the latter), were less satisfactory.

Both penotrane and cetrimide, however, had strong bacteriostatic activity, which made it difficult to prevent inhibition by small amounts of these agents transferred to culture media. It might be argued that this inhibitory mechanism should be enough also to prevent the growth of bacteria transferred from the skin treated with such an agent to an operation wound. By suitable dilution during sampling, however, organisms exposed to such skin treatment were found to grow in culture media, and the use of disinfectants which kill the skin flora must be regarded as preferable. In their detergent action cetrimide and other quaternaries have an advantage which is independent of their bactericidal action and is not shared with alcoholic chlorhexidine or iodine; we would suggest that such compounds should be used in place of soap and water for the mechanical cleansing of the skin before the application of the chosen skin disinfectant, which is left on the surface and allowed to dry.

It has been customary in many hospitals, and especially in orthopaedic practice, for the skin to be disinfected on three successive days as part of the pre-operative preparation. In our study we found that more than two treatments, each of two minutes, with 70% alcohol did not appear to add anything to what was achieved by two successive treatments (or sometimes even a single treatment) with alcohol. The rationale of disinfecting on successive days is uncertain. Staphylococci which are not removed at the first treatment may be regarded as resident organisms and can probably grow in the intervals between disinfection; for these, two treatments on the same day seem to be more useful than one treatment on each of two successive days. But if the skin is dirty and perhaps heavily

contaminated with spore-bearers that resist any form of skin disinfection, it is clearly desirable to allow time for the horny layer carrying these organisms to be completely removed before an incision is made. Under these conditions, the repeated application of a hexachlorophane soap or "phisohex" might be useful as a component of skin preparation. We did not include these agents in the present study because their action is slow, and speed is essential in an antiseptic for use on operation sites; for repeated use on the hands of surgeons and nurses a cumulative action such as that provided by hexachlorophane is more suitable (Lowbury and Lilly, 1960).

The part which skin disinfection plays in preventing sepsis and the importance of choosing the best antiseptic are matters for speculation. We do not know how often the introduction of skin flora is to blame for the appearance of post-operative sepsis. No antiseptic can be expected to remove all the resident bacteria, or even all of the staphylococci when these are present in the deeper layers of the skin; some of the resident flora are probably transferred to the wound at every operation. Normally these organisms cause no clinical infection, and even when *Staph. aureus* is introduced into a wound it seems that a million or more cocci must be present before pus can be formed (Elek and Conen, 1957). It is rational, therefore, to use an antiseptic which, without injuring the patient, will cause the largest reduction in the skin flora.

Summary

The effect on antiseptics on "transient" skin flora was studied by a method in which test organisms (*Staph. aureus*), allowed to dry on areas of skin, were exposed to the action of antiseptics. After two minutes' treatment no test organisms were found in areas treated with 70% ethyl alcohol, with aqueous solutions of chlorhexidine (0.5%), with Lugol's iodine (1%), or with an iodophore (virac). Appreciable numbers of test organisms survived after treatment with 0.1% aqueous phenylmercuric dinaphthyl methane sulphate (penotrane) and with 1% or 2% aqueous cetrimide.

Six antiseptics and a control were tested for their action in two minutes' treatment against "resident" skin flora by a hand-washing technique on seven subjects, using a Latin square design. Iodine (1%) in alcohol had approximately the same effect and were significantly more effective than the other antiseptics tested. In contrast with iodine, chlorhexidine does not appear to cause sensitivity reactions, and therefore seems to be more suitable for routine use as a skin disinfectant.

A majority of nurses carrying *Staph. aureus* on their hands lost approximately the same proportion of staphylococci as of total organisms when their hands were disinfected for one minute with 70% ethyl alcohol, suggesting that these organisms were present in the deeper as well as the more superficial layers of the skin.

Three successive treatments of the hands for two minutes with 70% ethyl alcohol produced no greater reduction in hand flora than two such treatments, and in some subjects no further disinfection was obtained after a single treatment.

We thank our colleagues at the Birmingham Accident Hospital for their co-operation; I.C.I. (Pharmaceuticals) for chlorhexidine digluconate; Ward, Blenkinsop and Co. for penotrane, and Ruson Laboratories for virac.

References

Barber, M., and Kuper, S. W. A. (1951). *J. Path. Bact.*, **63**, 65.
Calman, R. M., and Murray, J. (1956). *Brit. med. J.*, **2**, 200.
Elek, S. D., and Conen, P. E. (1957). *Brit. J. exp. Path.*, **38**, 573.
Fisher, R. A. (1942). *The Design of Experiments*, 3rd edition, pp. 68–78. Oliver and Boyd, Edinburgh.
Frisch, A. W., Davies, G. H., and Krippaehne, W. (1958). *Surg. Gynec. Obstet.*, **107**, 442.
Gardner, A. D. (1948). *Lancet*, **2**, 760.
—— and Seddon, H. J. (1946). Ibid., **1**, 683.
Goldberg, A. A., Shapero, M., and Wilder, E. (1950). *J. Pharm. (Lond.)*, **2**, 89.
Lowbury, E. J. L., and Lilly, H. A. (1960). *Brit. med. J.*, **1**, 1445.
Price, P. B. (1938). *J. infect. Dis.*, **63**, 301.
—— (1957). In *Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization*, edited by G. F. Reddish, 2nd edition, p. 399. Lea and Febiger, Philadelphia.
Story, P. (1952). *Brit. med. J.*, **2**, 1128.

HYDROFLUMETHIAZIDE DIURESIS IN HOSPITALIZED PATIENTS

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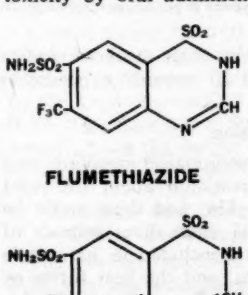
Since the discovery of the diuretic properties of chlorothiazide (Ford *et al.*, 1957) a number of chemically related compounds have been developed and introduced in the continuing search for an ideal non-mercurial oral diuretic agent. One of these new compounds is hydroflumethiazide, a trifluoromethyl derivative of a benzothiadiazine dioxide. Hydroflumethiazide differs from chlorothiazide in the presence of a trifluoromethyl group in place of the chloride group and two hydrogen atoms replacing the double bond in the thiadiazine ring. As may be seen from the formulae, hydroflumethiazide bears the same relationship in chemical structure to flumethiazide as hydrochlorothiazide does to chlorothiazide.

Experimental studies have demonstrated that hydroflumethiazide, administered orally to rats, induces a marked increase in the urinary excretion of sodium and chloride with much less effect on potassium, and that, on a weight basis, hydroflumethiazide is approximately 15 times as potent as chlorothiazide in producing a similar saluretic effect (Kobinger and Lund, 1958). Moreover, hydroflumethiazide possesses very low acute toxicity by oral administration to both mice and rats.



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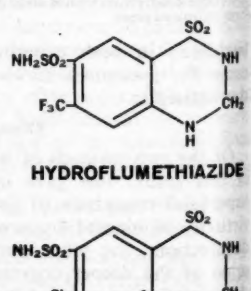

HYDROFLUMETHIAZIDE

CHLOROTHIAZIDE

HYDROCHLOROTHIAZIDE

and is less toxic to mice after single intraperitoneal doses than chlorothiazide (Kobinger and Lund, 1958).

Clinical studies have revealed that hydroflumethiazide is a potent diuretic agent when administered by mouth (Hobolth, *et al.*, 1958; Fuchs, 1959), that it is effective when given repeatedly (Dennis and Ford, 1959), and that its continued administration for six weeks or more causes no significant changes in serum electrolytes (Fuchs, 1959; Larson, 1959). On a weight basis, hydroflumethiazide appears to be at least 10 times as potent as chlorothiazide in diuretic action (Hobolth *et al.*, 1958; Dennis and Ford, 1959).

The present paper concerns the results of a clinical trial conducted at the University of Oregon Medical School Hospital to evaluate the efficacy of hydroflumethiazide (" di-ademil ") as a diuretic agent in the treatment of severe oedematous states. The principal parameters of observation included (1) clinical improvement in the condition of the patient; (2) loss in body weight; and (3) changes in the patterns of excretion and levels of serum electrolytes before, during, and after treatment with the drug.

Material and Methods

The Patients.—Twenty-six patients (25 males, 1 female) whose major symptoms were the result of salt and fluid retention were selected for study. Their ages ranged from 32 to 88 years. All had been in hospital because of the severity of the oedema present, and the acute nature of other underlying pathological states with which the oedema was associated. Most of the patients were suffering from congestive heart failure, including three who had cirrhosis with oedema and one who presented evidence of the nephrotic syndrome. Specifically, the conditions present in the patients with which oedema was associated were as follows: Congestive heart failure, 2; congestive heart failure with arteriosclerotic heart disease, 11; congestive heart failure with rheumatic heart disease, 5; congestive heart failure with luetic heart disease, 1; congestive heart failure with calcific aortic stenosis, 1; congestive heart failure with hypertensive cardiovascular disease, 1; cirrhosis of the liver, 1; cirrhosis complicated by congestive heart failure, 3; nephrosis, 1.

Procedure.—All patients were kept at bed rest; they received a diet which contained 1 g. of sodium and water *ad libitum*. Digitalis and all other medications except diuretics which were being received prior to admission were continued throughout the entire observation period. Whenever possible a period of three days was allowed to elapse after admission before hydroflumethiazide was begun, for stabilization of the patient. Some patients, however, required an immediate injection of meralluride when admitted. In these cases the single injection of mercurial was followed by a stabilization period of three days without diuretic. When indicated, the patients were first digitalized over a 24-hour period with oral digoxin and then allowed two days for stabilization. In four cases the patient's condition on admission was so acute that a waiting period of only 24 hours was possible before starting diuretic therapy. The body weight, blood-pressure, urinary volume, urinary electrolytes, and urinary *p*H were recorded daily before, during, and at the completion of treatment with hydroflumethiazide. Likewise, before, during, and after treatment, the concentrations of serum electrolytes (sodium, potassium, chloride, carbon dioxide) were determined, usually twice a week. The blood urea nitrogen was determined weekly. Three of the 26 patients could not be weighed because of their recent myocardial infarctions.

Medication.—Initially, the patients were started on a dosage of 50 mg. of hydroflumethiazide twice a day. In four the dosage was increased to 50 mg. three times a day. To two patients in the series prednisone and hydroflumethiazide were administered concomitantly because of the presence of reactivated rheumatic fever. Four others were treated with acetazolamide after treatment with hydroflumethiazide because of carbon-dioxide retention secondary to chronic obstructive emphysema or because of an observed rise in the levels of serum bicarbonate. The observations made during acetazolamide therapy have not been included in this report. Two other patients were transferred to meralluride after several days' trial of hydroflumethiazide had failed to produce diuresis. Treatment with hydroflumethiazide

TABLE I.—*Therapeutic Results in 26 Patients Treated with Hydroflumethiazide*

Case No.	Condition Presented	Age and Sex	Administration of Drug		Evaluation of Results	Remarks
			Dose (mg.)	Duration (Days)		
1	C.H.F.	83 F	100	5	Excellent	Marked loss of Na; oedema vanished; lost 16 lb. (7·3 kg.)
2	,,	84 M	100	6	,,	Excellent loss of Na; lost 16½ lb. (7·5 kg.) in 6 days; some K loss
3	,,	80 M	100	15	,,	Marked loss of Na; lost 30 lb. (13·6 kg.) in 14 days; increase in B.U.N.
4	,,	59 M	100	7	,,	Good loss of Na; low K loss; 22 lb. (10 kg.) lost in 6 days
5	,,	83 M	100–150	9	,,	Prompt and marked loss of Na; 35 lb. (15·9 kg.) lost in 9 days
6	,,	58 M	100	9	,,	Marked Na and Cl loss; 10 lb. (4·5 kg.) lost in 10 days
7	,,	54 M	100	7	,,	Marked Na and Cl loss; oedema-free in 4 days
8	,,	68 M	100	3	,,	Good loss of Na; 1½ lb. (0·7 kg.) lost in 1 day
9	,,	83 M	100	20	,,	Marked loss of Na; B.U.N. and uric acid rose, lost 36½ lb. (16·5 kg.) in 20 days
10	,,	73 M	100	8	Good	Good loss of Na; 8 lb. (3·6 kg.) lost in 8 days
11	,,	72 M	100	8	Satisfactory	Good loss of Na; 2 lb. (0·9 kg.) lost in 10 days
12	,,	83 M	100	6	Good	9 lb. (4·1 kg.) lost in 6 days; blood-pressure declined from 162/112 to 130/70
13	,,	84 M	150	7	Satisfactory	Good loss of Na but also some loss of K
14	,,	56 M	100	8	,,	Good loss of Na; 11 lb. (5 kg.) lost in 6 days
15	,,	88 M	100	7	,,	Good loss of Na but also marked K loss
16	,,	59 M	100	8	Fair	No loss of weight; some loss of Na and K
17	,,	42 M	100	4	Fair or poor	No loss of sodium; some loss of K
18	,,	73 M	100–150	14	Poor	Only transient loss of Na; rise in B.U.N. No diuresis or significant weight loss
19	,,	71 M	100	5	,,	No diuresis and no loss of weight
20	,,	59 M	100–150	8	,,	No loss of weight; oedema persisted; good loss of Na and Cl
21	,,	74 M	100–150	10	,,	No response because of advanced condition
22	Cirrhosis	55 M	100	7	Good	Salt loss but no weight loss; blood-pressure showed some decline; serum K low on 1st day
23	,,	69 M	100	3	,,	Patient " dry " when treatment began; therefore no loss of weight; good loss of Na
24	,,	79 M	100	6	,,	No loss of Na but 10 lb. (4·5 kg.) lost in 6 days
25	Nephrotic syndrome	32 M	100	9	,,	15 lb. (6·8 kg.) lost in 9 days
26	C.H.F.	56 M	100	8	,,	Prompt loss of Na; 4½ lb. (2 kg.) lost in 7 days

was continued for periods of from 3 to 20 days, with an average for the group of 8.1 days.

Results

In 24 patients, including three with hepatic cirrhosis complicated by congestive heart failure and one patient with nephrosis, the oedema was due primarily to congestive failure. Only one patient with cirrhosis did not have congestive failure. However, since the results obtained for these patients and the nephrotic patient all followed the same pattern, no separate categorization for their responses seemed necessary. Similarly, the results observed for the two patients who received prednisone have been included with those for the other groups, since they had been receiving prednisone for some time before the control and treatment observations were made.

Clinical Response

The clinical response was regarded as good or excellent in 16 of the 26 patients treated with hydroflumethiazide and satisfactory in four, while in the remaining six only fair or poor results were obtained (Table I). In the patients who showed "good" or "excellent" results the goals of therapy were achieved —that is, there was marked or good elimination of body sodium, a definite loss in body weight, and the disappearance of the oedematous condition present when treatment began. In the patients with "satisfactory" results a good diuretic and saluretic response to hydroflumethiazide was generally observed, with some improvement in the condition of the patients but not to the degree seen in the 16 patients with a good or excellent response to therapy. Little or no saluresis or improvement in symptoms was noted in the patients with "fair" or "poor" results.

Changes in Body Weight

Of the 23 patients whose body weights were determined (three coronary cases could not be weighed), 19 showed some loss of weight while four showed none (Table II). Of the 19 patients who lost weight during treatment, five lost at least 2 lb. (0.9 kg.) per day, nine lost at least 1 lb. (0.45 kg.) per day, and in five the loss was too small to be regarded as a satisfactory response to therapy. The loss in body weight of the 23 patients who could be weighed averaged 1 lb. (0.45 kg.) per day during the control period as compared with 1¼ lb. (0.6 kg.) per day during treatment.

TABLE II.—*Evaluation of the Response to Hydroflumethiazide According to Changes in Weight in 23 Patients**

Criteria			Results		
Daily Weight Loss		Evaluation	Average Weight Loss for Entire Period of Treatment		No. of Patients
lb.	kg.		lb.	kg.	
>2	>0·9	Excellent	3·2	1·45	5
1–2	0·45–0·9	Good	1·4	0·63	9
0·25–0·99	0·11–0·45	Poor	0·48	0·22	5
<0·25	<0·11	Failure	0·00	0	4

* Body weights could not be determined in three patients undergoing care for coronary disease.

Changes in Urine Electrolytes

The changes noted in the urinary volume and excretion of electrolytes before, during, and after the administration of hydroflumethiazide were subjected to statistical evaluation of variance for the determination of their significance (Table III). Hydroflumethiazide induced a significant increase in the excretion of urinary sodium and chloride in most of the treated patients, which for the series as a whole equalled the control values. Excretion of urinary water was comparable to that seen with bed rest in some patients; in others the urinary volume increased, though to a less degree than did either urinary sodium or chloride excretion. A significant increase in the average urinary excretion of potassium occurred only in the 12 patients who had had an initial three-day period of bed rest, digitalization, or continued digitalis therapy and low-salt diet before starting hydroflumethiazide (group I, Table III). In this group the average loss of potassium was approximately 1.5 times that of the pretreatment level.

Patients who had received only bed rest and low-salt diets (group I, Table III) or meralluride (group II, Table III) exhibited proportionally the same increase in the amount of fluid and electrolytes excreted during therapy over that shown during the first and third days, respectively, of the pretreatment period. This finding for group II suggests dissipation of the major effect of the mercurial diuretic by the third day after injection. Maximum sodium and chloride excretion was usually effected by the second or third day of therapy, as shown in the graphed results of two patients (Figs. 1 and 2). In three patients, however, excretion of these electrolytes reached a peak after six days of treatment. In three other cases the excretion of urinary sodium dropped during treatment with hydroflumethiazide, but there was a concomitant rise in the excretion of urinary

TABLE III.—*Average Increase in Urinary Water and Electrolyte Excretion and Accompanying Average Concentrations of Serum Electrolytes During Hydroflumethiazide Therapy*

Patient Group	No. of Patients	Urinary Excretion (Average)					Serum Electrolytes (Average)				
		Observation Period	Volume (ml.)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Observation Period	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Bicarbonate (mEq)
I. Initial 3-day stabilization period (bed rest, digitalis, salt-free diet)	12	Control	1,435	39·2	22·0*	46·5	Control	127	4·1	101·4	23·6
		Increase (aver.) over control	+360	+39·5	+13·6	+53·9	Therapy	122·5	4·2	98·0	26·4
II. Meralluride injection on entry plus procedure for group I	10	Control	1,170	51·7	30·1*	32·8	Control	126·5	4·0	101·0	23·7
		Increase (aver.) over control	+307	—†	—	58·1	Therapy	128·7	1·0	100·0	27·2
III. Hydroflumethiazide started within 24 hours after entry	4	Control	1,825	None	None	None	Control	125	4·3	105·0	22·0
		Increase (aver.) over control	—	—	—	—	Therapy	121	4·4	94·0	25·6
IV. Combined results for groups I, II, and III	26	Control	1,330	44·1	25·0	41·1	Control	127	4·1	100	23·8
		Increase (aver.) over control	+339	+35·9	—	+55·5	Therapy	125	4·1	96	26·7

* Three patients in group I and two patients in group II had been receiving supplemental potassium, which was discontinued on entry.
† Where no value (—) for urinary volume or electrolyte excretion is reported the results were not statistically significant. All other values shown in this category are statistically significant as measured by 95% confidence limits. No control urinary electrolyte measurements were made for group III.

potassium. Of the four patients (group III, Table III) whose condition on admission did not permit a waiting period of three days before initiation of diuretic therapy, two exhibited patterns of excretion during treatment with hydroflumethiazide similar to those seen in patients of groups I and II; in the other two cases there was little or no diuretic response to therapy.

Changes in Serum Electrolytes

In the majority of patients treatment with hydroflumethiazide was followed by a rise in serum bicarbonate accompanied by a consistent acid-reacting urine. In two patients the serum bicarbonate remained elevated for periods up to two weeks after completion of therapy, then the administration of acetazolamide produced an immediate return of the concentration of serum bicarbonate to the upper limits of normal. It was noted that in a few patients with elevated serum bicarbonate the administration of acetazolamide after hydroflumethiazide induced a further diuresis with further loss in body weight and a prompt return of the serum bicarbonate to normal limits. Other serum electrolytes were not changed significantly during therapy with hydroflumethiazide although there were several instances of reduced levels of serum sodium and serum chloride, and in one case serum potassium declined below the lower limits of normal. This patient also exhibited an excessive urinary excretion of potassium without any increase in the excretion of urinary sodium.

Other Observations

Blood urea nitrogen levels rose in seven patients, although this rise was not necessarily attributable to the administration of hydroflumethiazide. While all seven patients exhibited increased excretion of urinary water and electrolytes, the loss in body weight was not marked.

Blood-pressures declined to normal or near normal levels* in each of seven patients whose diastolic pressure had been 90 mm. Hg or higher before treatment began. Blood-pressures declined by 10 to 30 mm. Hg systolic and 10 to 20 mm. Hg diastolic in approximately half of the remaining patients in the series, but these changes were without apparent clinical significance. Because of the abnormal range of control uric acid values in the patients under study, this biological parameter was not evaluated.

In both of the patients with active rheumatic heart disease who received combined steroid–hydroflumethiazide treatment, the excretion of urinary sodium and chloride, as well as the loss in body weight, exceeded the overall average for the series.

In three patients therapy was terminated prematurely by death. One experienced a myocardial infarction, another developed bronchopneumonia terminal in 24 hours, and the third suffered a fatal ventricular arrhythmia.

Figs. 1 and 2 demonstrate the individual response to treatment with hydroflumethiazide in two representative patients.

Case 1.—A white woman aged 88, with a history of progressive cardiac decompensation for the preceding three months, was given an injection of meralluride immediately upon admission because of the severity of her condition, put to bed, and continued on digitalis and a low-salt diet. Despite the initial mercurial injection, the patient showed a rather profound response to hydroflumethiazide (Fig. 1). There was some depression of the levels of serum sodium.

Case 2.—A white man aged 84 entered hospital with congestive heart failure secondary to arteriosclerotic heart disease. He had a history of gradual cardiac decompensation extending over a period of two and a half months. On admission he was placed on bed rest, low-sodium diet, and digitalis for three days before treatment with hydroflumethiazide was begun. The discrepancy between the loss of weight and urinary output recorded for this patient (Fig. 2) was traced to poor fluid intake. Noteworthy is the rising blood urea nitrogen, which began to increase at about the time when the patient's weight became stable. (Fig. 2 shows results for the third day of the control period.)

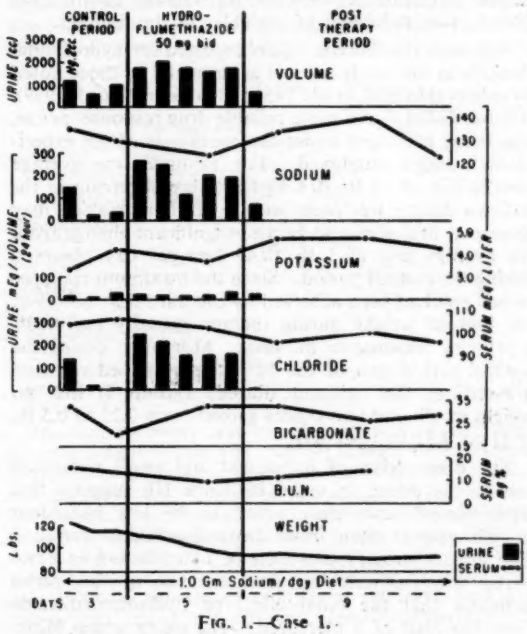

FIG. 1.—Case 1.

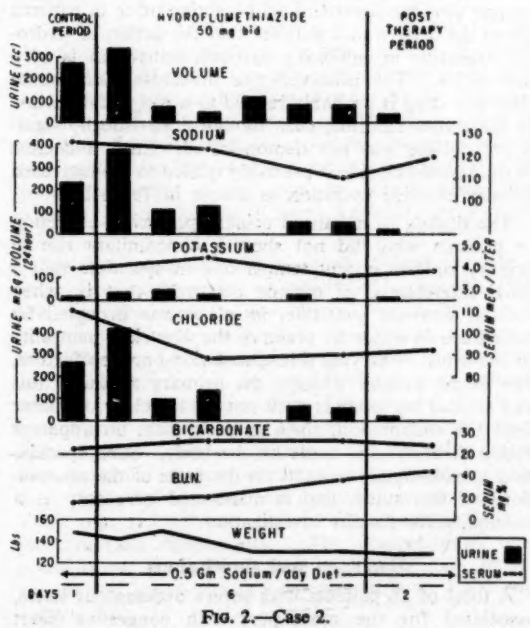

FIG. 2.—Case 2.

*Blood-pressure of 150/90 mm. Hg or less.

Discussion

Whenever a study of a specific change within a biological system such as man is undertaken a multiplicity of variables must be considered. To make the observations more reliable, standardization of the system is desirable. In the present study a three-day period was allowed to elapse, whenever possible, before initiation of therapy with the diuretic drug under trial, since the maximum diuretic effect of bed rest and inactivity should accrue within this period. Furthermore, such a period for stabilization of the patient before treatment began permitted the use of each patient as his or her own control, thereby contributing to a further reduction of variables in the findings.

Although the diuretic results reported for hydroflumethiazide in this study are not as dramatic as those noted by others (Hobolth *et al.*, 1958 ; Dennis and Ford, 1959), it is our belief that a more reliable drug response, *per se*, was being measured under the conditions of the experimental design employed. For example, the average weight loss of 1¼ lb. (0.6 kg.) per day occurring in the patients during treatment with hydroflumethiazide may appear at first glance to be an insignificant change from the average loss of 1 lb. (0.45 kg.) per day observed during the control period. Since the maximum response to bed rest had been achieved by the third day, however, the loss of weight during therapy actually represents a primary response to the drug. Moreover, during the control period two of the 12 patients on bed rest and low-sodium diet without diuretic (group I) lost no weight at all, and two others gained from 0.25 to 0.5 lb. (0.11 to 0.22 kg.) per day.

The observation of infrequent and small potassium loss in the urine, as noted in Table III, suggests that hydroflumethiazide may prove to be less hazardous in this respect than other benzothiadiazine diuretics. The greater urinary excretion of chloride ion as compared with sodium ion demonstrated in this series indicates that the renal effect of hydroflumethiazide resembles that of a mercurial. The rising serum bicarbonate plus the consistent acid-reacting urine in patients given the drug would indicate that the action of hydroflumethiazide in inhibiting carbonic anhydrase is of a low order. The observed rise in serum bicarbonate with this drug is probably related to a reciprocal decline in the serum chloride, even though a statistically significant decline was not demonstrated. Such a decline in the serum chloride is probably related to the increased urinary chloride excretion as shown in Table III.

The finding of enhanced urinary potassium excretion in patients who did not show a concomitant rise in urinary sodium output tempts one to speculate that a renal interchange of cations occurred—that is, when sodium was not available, its place was occupied by potassium in order to preserve the electrical neutrality of the urine. Carrying this speculation one step further, one might wonder whether the primary action of this and similar compounds were not on the chloride rather than the sodium ion, since in such cases no apparent cation distinction is made by the body. Such speculation is exceedingly tenuous on the basis of the observations of this study, and is mentioned here only as a possibility for further investigation.

Summary and Conclusions

A total of 26 patients with severe oedematous states, associated for the most part with congestive heart failure, have been treated with a new diuretic agent, hydroflumethiazide, in daily doses of 100 to 150 mg. for from three to 20 days. Good or excellent clinical results were observed in 16 of the 26 patients, manifested by increased elimination of urinary sodium, loss in body weight, and disappearance of oedema. Satisfactory results were seen in four patients, while in the remaining six treatment failed. Three patients died during therapy. One suffered myocardial infarction, another experienced a fatal ventricular arrhythmia, and the third developed bronchopneumonia, terminal in 24 hours.

A three-day period of bed rest, with digitalization when indicated or continuance of digitalis, low-sodium diet, and water *ad libitum*, was allowed to elapse before beginning therapy with hydroflumethiazide to eliminate bed rest as an experimental variable.

Hydroflumethiazide induced a significant increase in urinary sodium and chloride excretion which equalled the control levels. Urinary water excretion also was increased in some patients, although not to the degree as were urinary sodium and chloride. Significant increase in loss of urinary potassium occurred much less often with hydroflumethiazide than did that of other urinary electrolytes. When potassium loss was noted it approximated 1.5 times the pretreatment levels.

Hydroflumethiazide also induced an elevation of serum bicarbonate, a condition which sometimes persisted for two weeks or more unless treated with a carbonate anhydrase inhibitor. A prompt return of serum bicarbonate to normal levels occurred after treatment. No significant changes of other serum electrolytes were generally encountered.

Hydroflumethiazide is a potent saluretic agent with less tendency to induce hypopotassaemia than some other benzothiadiazine diuretic compounds.

References

Dennis, E. W., and Ford, R. V. (1959). *Clin. Res. Notes*, **2**, No. 7, 1.
Ford, R. V., Moyer, J. H., and Spurr, C. L. (1957). *A.M.A. Arch. intern. Med.*, **100**, 582.
Fuchs, M. (1959). *Clin. Res. Notes*, **2**, No. 7.
Hobolth, N., Thomsen, K., From Hansen, P., Hägensen, N. R., and Opresnik, J. (1958) *Ugeskr. Læg.*, **120**, 1585.
Kobinger, W., and Lund, F. (1958). Ibid., **120**, 1583.
Larson, E. (1959). *Clin. Res. Notes*, **2**, No. 7.

The United Kingdom Atomic Energy Authority has published a revised and almost completely rewritten edition of its *Guide to U.K.A.E.A. Documents*, which has been out of print for some time. The *Guide* explains to the public how the Authority publish information about their research, development, design, and other work, and where new publications are announced ; how the Authority is organized into various autonomous groups, and by which of their establishments information is published ; and where the public can obtain free access to read the publications—at depository libraries in Great Britain and 36 foreign and Commonwealth countries—or where they can buy them. A good deal of background information about various series of technical reports, from the early days of the Ministry of Supply, is also given for the many libraries with collections of them. Among the new features of this edition are details of a sales service of scientific and technical reports, operated by the Authority, whereby the public may place standing orders for those on particular subjects ; a further sales service operated by a Wakefield firm under contract, which provides microcopies of older or out-of-print reports ; and a list of bibliographies of atomic-energy literature, compiled by the Group's libraries, available to the public. Copies may be purchased from H.M. Stationery Office or from any bookseller at 1s. 6d. net.

SYMPATHETIC BLOCKADE IN TREATMENT OF HYPERTENSION

CLINICAL TRIAL OF BRETYLIUM TOSYLATE

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Ten years ago, in papers on medical sympathectomy and the clinical use of methonium compounds, early experience in this unit with ganglion-blocking drugs was recorded (Turner, 1950, 1951). Recently the indications for treatment, method of administration, and the problems of tolerance and side-effects were reviewed (Turner, 1959).

At an early stage it was decided that to initiate life-long treatment with potent and potentially dangerous drugs was a major decision and that it was best first to make a detailed and standardized assessment of each patient in hospital. If treatment was indicated we tried to achieve a steady state with the appropriate drug, and then further treatment was supervised on a long-term basis in a special clinic organized for the purpose. This procedure has helped to ensure the proper and uniform selection of patients suitable for treatment, has facilitated the maintenance of good control over the blood-pressure as well as the collection and correlation of data, and has made possible comparative assessments of different drugs. Numerous ganglion-blocking agents have been investigated, all potent in lowering the blood-pressure, but none free from difficulties of administration, particularly as regards tolerance and side-effects. None, in fact, has been satisfactory.

Although the blood-pressure can be reduced to almost any desired level this can rarely be achieved without troublesome side-effects from concomitant parasympathetic blockade. Some improvement results from combining the ganglion-blocking drug with chlorothiazide or rauwolfia, but in some degree most patients complain of constipation, dryness of the mouth, difficulty with accommodation, delay in micturition, or impotence. In many individuals these effects are associated with a feeling of general malaise. Because of all this, physicians have looked forward to the day when research workers would be rewarded by the finding of a compound with selective blocking action on the sympathetic nervous system.

Recently, in the laboratories of the Wellcome Foundation in England and the Ciba Foundation in Switzerland, compounds have been isolated which do selectively block the peripheral sympathetic nervous system by accumulating in sympathetic ganglia and post-ganglionic fibres.

The first of these has been given the name of bretylium tosylate ("darenthin"), and has the formula N-*o*-bromobenzyl-N-ethyl : N : N-dimethylammonium *p*-toluenesulphonate. The second substance has been given the name of guanethidine ("ismelin") and has the formula 2-(octahydro-L-azocinyl-ethyl) guanidine sulphate.

This paper is principally concerned with a clinical trial of bretylium, which we have used for 15 months in the treatment of 43 patients with hypertension.

Material and Method

Our selection of cases, measurement of blood-pressure, and general principles of administration have been similar to those previously described and will not be elaborated here. Only those patients were treated who, in addition to high diastolic pressures, had objective evidence of secondary changes in the fundi or heart. Brief clinical details are shown in Table I.

TABLE I.—*Clinical Details* (43 *Cases*)

		No. of Cases
Method of Presentation	Left ventricular failure	12
	Cerebro-vascular accident	9
	Headache	7
	Disturbance of vision	6
	Routine examination	6
	Miscellaneous	3
Diastolic Blood-pressure	Blood pressure 130+	40
	,, ,, 120–129	2
	,, ,, 110–119	1
Retinal Changes	Grade 4	8
	,, 3	11
	,, 2	21
	,, 1	3
Left Ventricular Hypertrophy (E.C.G.)	Present	39
	Absent	4
Renal Function	Impaired function	9
	Renal failure	2
	Normal function	32

The blood-pressure was recorded after the fourth consecutive inflation of the cuff. Retinal changes were classified according to the criteria recommended by Keith, Wagener, and Barker (1939). Criteria for left ventricular hypertrophy were those recommended by Sokolow and Lyon (1949). Cohsiderable ventricular hypertrophy may develop before this is reflected in the electrocardiogram. Renal failure denotes a blood urea above 40 mg. per 100 ml. Impaired renal function denotes an endogenous creatinine clearance below 100 litres/24 hours or phenolsulphonephthalein excretion below 20% in 15 minutes.

For the purpose of assessing the drug the fall in blood-pressure was taken as the sole criterion of therapeutic effect. Many of thse patients had been previously treated with ganglion-blocking drugs. As the basis for selection of patients and general method of treatment in our clinic has been unchanged for ten years we believe it is possible to compare the result of this trial with those previously carried out for other drugs—for example, mecamylamine (Kitchin, Lowther, and Turner, 1957).

The initial dose was 100 mg. (half-tablet), given three times daily after meals, and daily increments of 100–300 mg. were made at intervals of two to three days. In patients who are under close observation in hospital the dose can be increased to 6 tablets a day quite quickly, but caution is necessary because some patients are far more sensitive than others, and we have encountered syncope from postural hypotension with a daily dose as small as 300 mg. On the other hand, some patients are very resistant to treatment, and the daily dose may have to be increased to as much as 3,000 mg. (15 tablets) before the standing diastolic pressure falls significantly. The average daily dose given to our group of patients was 2,000 mg. In one patient the blood-pressure was resistant to 6,000 mg. a day.

Results

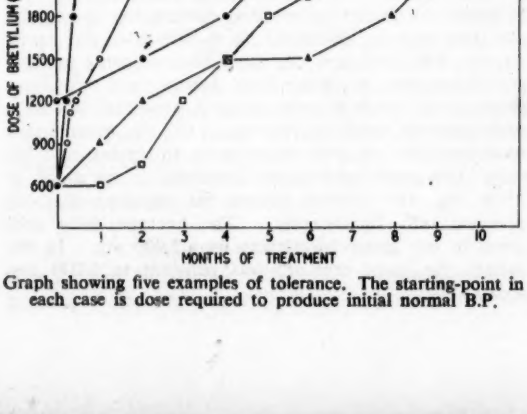
The results have been classified into "good," "fair," and "poor" groups. A good result is claimed when the blood-pressure is reduced by 30/20 mm. and the diastolic pressure to below 100 mm. A fair result is claimed when the blood-pressure is reduced by 30/20 mm. and the diastolic pressure to 100/110 mm. Where there was no appreciable hypotensive effect throughout the period of trial the result was graded poor.

On this basis, 8 patients (19%) after an average period of six months show good results, 8 patients (19%) show fair results, and 27 patients (62%) are graded as poor. By the rather less strict criteria described by Dollery, Emslie-Smith, and McMichael (1960) 38% of results would be graded as good, but this entails accepting a reduction of 20 mm. Hg or more as a good result even though the diastolic pressure remained high. By either standard these results cannot be regarded as satisfactory for patients with severe hypertensive disease and for treatment which necessitates frequent visits to a clinic because of the development of tolerance, which imposes a new set of unpleasant side-effects, and which may, after dose increments extending over several weeks, be entirely ineffective owing to resistance. Treatment with bretylium has in fact now been abandoned in 35 (81%) of our patients. It is emphasized that "good" results, by whatever criteria they are judged, represent merely the blood-pressure response and do not imply that bretylium is a satisfactory therapeutic agent in other aspects.

In fact, the major disadvantages of tolerance, variability of response, and syncope render it not only a disappointing hypotensive drug but sometimes also a dangerous one. When the additional disadvantages of side-effects, resistance, and sensitivity are added it is clear why treatment with bretylium has had to be abandoned in so many patients, and our decision not to use the drug for new patients seems amply justified. These disadvantages merit consideration in rather more detail.

Tolerance

Boura *et al.* (1959), in their original paper, predicted that tolerance was likely to develop. Our experience and that of others has shown that this effect, despite the advantages of freedom from parasympathetic blockade, largely vitiates the value of the drug.



Graph showing five examples of tolerance. The starting-point in each case is dose required to produce initial normal B.P.

A preliminary fall in pressure occurs in most cases, but when kept under observation for several months a high proportion of patients (74%) required a steady increase in dose in order to maintain control, if indeed control could be maintained. Patients treated with bretylium must thus continue under the close supervision which has been necessary with other drugs. Despite reassurance, these repeated increases inevitably engender disappointment and depression at successive attendances, and when side-effects are also troublesome much persuasion is required to induce patients to continue. In addition, repeated visits to hospital at short intervals lead to administrative difficulties in running the clinic.

As can be seen from the Graph, tolerance tends to develop early and to increase at varying speeds. Thus, for these patients it is not advisable to extend the period between visits beyond a few weeks. Apart from these disadvantages, tolerance results in ineffective treatment over long periods, and in the end, despite perseverance by patient and doctor, control is often lost. In patients with severe hypertensive disease delay in controlling the blood-pressure may be dangerous.

The rapid development of tolerance may lead to sudden loss of control between visits to the clinic, with serious consequences in patients with severe hypertension. Two of our patients died on this account. It may be, as has been suggested, that some degree of tolerance is inevitable with drugs acting at the neuromuscular junction, but initial experience with guanethidine suggests that with other compounds it may at least be less.

Our early experience in regard to tolerance (Turner and Lowther, 1959) was soon confirmed by others (Evanson, 1959; Dollery, 1960; Dollery *et al.*, 1960; Somers, 1960), and since then numerous workers with whom we have compared experience have noted the same effect.

Variable Response

In some patients, probably owing to varying absorption, the blood-pressure fluctuates considerably from hour to hour, and, as a result, symptoms arising from hypotension may appear unpredictably and lead to feelings of insecurity and apprehension. We have made estimations of the blood-pressure at hourly intervals in patients on bretylium, and have found on many occasions swings of pressure which make it clear that it is impossible to control dosage with reference to single pressure estimations such as may be recorded in the consulting-room or out-patient clinic, even if pressure is recorded at the same time of day on each occasion. This is of especial importance in those patients in whom dosage is critical, and in whom even a small change may result in considerable alterations of the blood-pressure. Examples of instability of response are shown in Table II.

It is emphasized that our recordings are taken under uniform circumstances and by the same observer after the patient has been standing for a period of three minutes.

TABLE II.—*Showing the Variations in Standing Diastolic Blood-pressure (mm. Hg) from Hour to Hour in 7 Patients Taking Bretylium*

	1	2	3	4	5	6	7
10 a.m.	140/110	140/105	170/95	140/115	180/115	190/115	200/140
11 ,,	100/80	200/120	170/115	175/125	130/95	200/125	150/115
12 noon	110/95	130/95	195/125	175/145	150/115	180/105	180/135

Syncope

Syncope must be included amongst the major disadvantages of bretylium, and in our experience is more troublesome than with any other drug, principally because it may develop so rapidly and quite apart from postural hypotension. Syncope, especially on exertion, may occur without warning, and potentially is exceedingly dangerous. It has occurred in six of our patients. One woman walked up five flights of stairs in a department store and lost consciousness at the top. An actuary left the clinic feeling well, walked down the drive, and hurried over the road to catch a bus. He suddenly lost consciousness and was nearly run over. Two others fell down in the street. Another patient, while sitting in a chair, twice lost consciousness, which, although relatively safe, caused great anxiety. In none of these patients was the standing diastolic pressure, when last recorded, below 115 mg. Hg. Other workers have reported similar effects (Lowe and Rosenheim, 1960).

Evidence that exertion may lead to a sharp fall in cardiac output in patients taking bretylium has recently been presented by Taylor and Donald (1960), and it seems that this is the causal mechanism in some patients. In other cases exertion has not been involved, and the mechanism here is more obscure. We have not seen dangerous complications from postural hypotension, but others have been less fortunate (Dollery *et al.*, 1960).

Side-effects

Side-effects, though numerous and often troublesome, are relatively mild compared with those which are associated with ganglion-blocking drugs, and it is this fact which gives rise to initial enthusiasm in patients who are transferred from one drug to the other.

The registration of side-effects is one in which individual practice varies widely. Some believe that the patient should be asked only in general terms how he or she feels, and that questioning at once obtrudes the beliefs and prejudices of the observer. Others approach the patient armed with a list of potential side-effects, and lay themselves open to the charge of suggestion. While there is no doubt that the frequency of any observation depends on the diligence with which it is sought, it is unlikely that many patients actually fabricate complaints, and if the numbers under observation are large enough and the symptoms are of similar type this latter objection becomes of little importance. We ourselves approached patients on bretylium with no set idea of what side-effects might occur, and indeed early in our experience attributed certain complaints to neurosis. It was only as these recurred with increasing frequency and fell into the same patterns that it became obvious that the effects were attributable to the drug. Subsequently some patients were questioned more directly—for example, as to whether any effect had been noticed on bowels or bladder or any odd sensations about the body. It became clear that many patients had not mentioned side-effects because they had regarded them as irrelevant, and others were more impressed by relief from the unpleasant effects of ganglion-blocking drugs.

Side-effects occurred in 39 out of the 43 patients, and would often have been tolerated if bretylium were a more effective hypotensive agent. Side-effects are generally more frequent in the early stages of treatment, and tend to diminish in importance as time passes. This may, of course, be due to the fact that the patient learns to live with them, and accordingly they slip below the threshold of consciousness. Certain complaints, however, are painful and persist, and may become worse with successive increments in dosage. This is particularly true of parotid pain. About twenty different side-effects have been reported, and our patients have experienced most of them (Table III).

TABLE III.—*Side-effects of Bretylium* (43 *Cases*)

Symptoms	No. of Cases
Dizziness (not due to posture)	23
Chest constriction or paraesthesiae	15
Frequency of micturition	15
Parotid pain	17
Dyspnoea	13
Diarrhoea	9
Headache	11
Muscular weakness	12
Syncope	6
Nasal congestion	12
Sweating	7
Tinnitus	4
Sexual difficulties	2
Nausea	2
Psychosis	1
Nil	4

Dizziness is a frequent complaint which is not related to postural hypotension, and not always to exertion. The cause may not be the same in all cases. The fall in blood-pressure caused by exertion in patients taking bretylium, to which attention was first drawn by Lowe and Rosenheim (1960), is a likely cause in some, and further exercise might result in syncope. In others, however, dizziness may occur while at rest or when doing nothing in particular. Dizziness tended to occur most often in the early stabilization stage of treatment, but it does tend to recur with any increment in dose in some patients, and eventually may prevent reaching the dose required to achieve full control of the blood-pressure.

Constriction in the chest is an unpleasant sensation which may simulate angina pectoris, but we have not yet been able to demonstrate evidence of myocardial ischaemia, and in most cases the probable cause lies in the chest wall. *Paraesthesiae*, especially in the form of "hot" sensations in the skin, are common over the front of the chest, but may also occur elsewhere.

Frequency of micturition is a common complaint and occurs usually at night in both men and women. This complaint tends to persist, but has not been sufficiently troublesome to require stopping the drug.

Parotid pain is a new and interesting drug-effect which has troubled about 40% of our patients. It is one of the symptoms which may persist beyond the stabilization period, and, in fact, is relatively infrequent in the early stages. Pain is centred just behind the mandible, and usually occurs once with the first bite of a meal or even of a sweet, and lasts for only a few seconds. It is occasionally of considerable severity. It cannot be produced by mere clenching of the teeth, nor is it produced by anticipation of food. There is no subjective increase in salivation. The pain occurs at rest, and there is no relationship to fall in blood-pressure.

Some patients have a continuous dull ache with tenderness in the region of the parotid gland. Patients who develop tolerance may nevertheless continue to complain of pain. Pain may persist for weeks or months if treatment is changed to guanethidine, and we know of one patient in whom it has persisted for several months after stopping all treatment. The mechanism of parotid pain is at present obscure. The

most likely explanation would seem to lie in increased secretion against resistance, such as might be produced by contraction of the smooth muscle in the duct, but it is difficult to fit in all the features mentioned above. We understand that attempts are being made to solve the problem by pressure-flow studies.

Dyspnoea on effort is a definite entity which occurs in about 30% of patients. There is no complaint of paroxysmal dyspnoea, nor is there any radiographic evidence of pulmonary oedema. No evidence of bronchospasm has been found on clinical examination, but one patient specifically complained of wheezing. The dose producing this side-effect may be critical, and in some patients the effect can be made to appear and then disappear by adding and withdrawing as little as 300 mg. of the drug daily. Dyspnoea may appear as an augmentation of existing dyspnoea or it may arise in a patient with no previous history of breathlessness. Pulmonary function and haemodynamic studies may well elucidate the pathogenesis of this symptom. Taylor and Donald (1960) have shown in acute experiments that bretylium may induce considerable pulmonary arterial hypertension.

Diarrhoea.—In striking contrast to the effects of ganglion-blocking drugs, some looseness of the bowels may occur, but this has not been severe or of such frequent occurrence as with guanethidine.

Headache may be produced in patients who had not previously had this complaint as a manifestation of their hypertension nor had been particularly subject to it in the past. In some it tends to persist.

It is noteworthy that certain of the complaints tabulated are those which might be expected to occur as a result of parasympathetic overactivity. Side-effects may also vary from patient to patient but tend to continue in the same pattern for each patient. These facts recall the observations of Paton and Steinberg (1956), who injected hexamethonium into 50 students from University College Hospital. Objective studies were made as regards ten autonomic tests, and the pattern of response was found to be different in every one. The similar variation in response which was found clinically with bretylium also reflects the difference in autonomic constitution between individuals.

Muscular Weakness.—This is an interesting complaint which can probably be explained on the basis of the experimental observations of Boura and Green (1959), in which it was shown that in rats and in cats paralysis occurred at the neuromuscular junction, and that when bretylium was given in a dose of 50 mg./kg. to monkeys muscular power was decreased.

Mental Changes.—One patient in our group previously unaffected by any form of mental instability developed a severe anxiety state, with depression, on being changed from pempidine to bretylium, and had to be admitted to a mental hospital. There has been no recurrence on guanethidine. Other workers have experienced a higher incidence of mental changes (Evanson and Sears, 1960).

Sexual Difficulties.—We have not made a particular point of inquiring about sexual difficulties, and few patients make spontaneous observations on this aspect. However, one practitioner noted undoubted and very considerable reduction in the volume of semen, one patient was much disturbed by loss of libido, and another by impotence.

Resistance

Resistance occurred in three patients, all with severe hypertension. This implies that there was no fall in standing blood-pressure despite a steady increase of dose to high levels—6,000, 4,800, and 3,000 mg. respectively. The effect of this practical defect was waste of time and the risk of potential complications from continued hypertension, and in the end a new drug had to be used.

Sensitivity

Exceptional sensitivity occurred in three patients, and in each a profound fall in blood-pressure resulted from a dose of 100 mg. (half-tablet) three times daily. It is therefore important to start with a small dose, such as 100 mg. twice daily, and gradually work up.

Bretylium in Combination

In four patients in whom control was impossible on bretylium alone, pempidine was added in small doses (2½–5 mg. t.d.s.). Larger doses were not used because of the development of side-effects from parasympathetic blockade. As a result control of the blood-pressure became classified as good in two, fair in one, and one was unchanged at poor. In four other patients chlorothiazide was added in a dose of 250 mg. three times daily, but this combination failed to influence the pressure to an appreciable extent. We did not persevere with this combination owing to the disadvantages of bretylium.

Guanethidine

After six months of a pilot trial it became clear that bretylium was not a suitable preparation for the treatment of the majority of patients with severe or moderately severe hypertension. Accordingly it was decided to continue only with those in whom it was still proving reasonably satisfactory and gradually to switch the others to guanethidine. By this means the effects of the two drugs could be compared in the same patients. It was also decided to start a pilot trial of guanethidine in patients with hypertensive disease of similar severity to those begun on bretylium.

Now after more than twelve months' experience with bretylium and six months' experience with guanethidine it seems probable that the latter preparation, though not ideal, is superior, and that a formal comparative trial would not be profitable or justifiable.

So far tolerance has been less troublesome and side-effects milder with guanethidine than with bretylium, and almost all patients who have had both drugs prefer the former. Experience is too limited in time and the numbers of patients too small to be dogmatic about the absolute value of guanethidine. Nevertheless, our present impression is that guanethidine is a better preparation for the treatment of hypertension, but in relatively resistant cases and in those who develop looseness of the bowels it should be combined with a ganglion-blocking drug in small dosage. It has not been established that for severe cases it is superior to a combination of a ganglion-blocking drug with chlorothiazide.

Conclusion

There is no doubt that the advent of a blocking substance with a selective action on the sympathetic division of the autonomic nervous system is an important event in physiological research, and from the pharmacological aspect opens up possibilities for a new

era in treatment. From the clinical point of view bretylium tosylate itself has proved disappointing.

In a series of 43 patients tolerance has been experienced in two-thirds, bringing attendant failure, disappointment, and even death as the patient passes out of control. We have found exceptional sensitivity in some, which indicates that treatment must be begun with a very small dose at first, and exceptional resistance in others, which results in the waste of weeks or months in hospital while stabilization is sought with a steadily increasing dose. We have found many side-effects which might be bearable were the treatment more effective, but which, combined with tolerance, sensitivity, and variable absorption must convince the most optimistic that in bretylium there is no new hope for hypertensive patients. In particular, recurrent dizziness and syncope are effects which no clinician can be willing to impose upon his patient.

While bretylium will produce a fall in blood-pressure in almost all patients the pressure can be safely and comfortably maintained at reasonable levels in only a very few, and certainly not in those with severe or malignant hypertension. We certainly agree with the Hammersmith workers that bretylium is not the drug of choice for patients with severe hypertension. Since none of the more potent drugs yet produced is sufficiently safe or free from side-effects to justify treating patients with mild hypertension, the only ones for whom it might be considered are those with hypertensive disease of moderate severity or in whom only a moderate lowering of blood-pressure is desirable. However, tolerance develops so frequently that treatment should not be persisted in for long. Thus, although the research workers can be congratulated for their breakthrough into a new field of autonomic blockade, bretylium tosylate is not a practical and effective therapeutic agent, and may, in fact, jeopardize the patient's life. In our opinion it should not be used for the treatment of hypertension. Initial experience with guanethidine has been more encouraging.

Summary

Forty-three patients with hypertension of a severity sufficient to cause secondary changes in the retinae or heart have been treated with bretylium tosylate for an average period of six months.

A short-lived fall in blood-pressure was usually found, but in two-thirds of these patients tolerance developed and the blood-pressure rose again despite steady increases in dose.

Side-effects were frequent, including dizziness, parotid pain, dyspnoea, and syncope, the last being a potentially dangerous end-result.

Some patients showed sensitivity to doses of 100 mg. t.d.s., and a few were resistant to doses rising to 6,000 mg. daily.

It is concluded that bretylium tosylate should not be used for the treatment of hypertensive patients.

Our thanks are due to Miss Norma Millar, our technician, who recorded with painstaking accuracy and good humour the very large numbers of blood-pressures upon which this study is based.

REFERENCES

Boura, A. L. A., and Green, A. F. (1959). *Brit. J. Pharmacol.*, **14**, 536.
—— Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
Dollery, C. T. (1960). Symposium on Adrenergic Mechanisms, organized by the British Pharmacological Society, London, March 28. Proceedings in press.
—— Emslie-Smith, D., and McMichael, J. (1960). *Lancet*, **1**, 296.
Evanson, J. M., and Sears, H. T. N. (1960). Ibid., **1**, 544.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
Kitchin, A. H., Lowther, C. P., and Turner, R. W. D. (1957). *Lancet*, **2**, 605.
Lowe, R. D., and Rosenheim, M. L. (1960). Ibid., **1**, 655.
Paton, W. D. M., and Steinberg, H. (1956). *Brit. med. J.*, **2**, 622.
Sokolow, M., and Lyon, T. P. (1949). *Amer. Heart J.*, **37**, 161.
Somers, K. (1960). *Lancet*, **1**, 981.
Taylor, S. H., and Donald, K. W. (1960). Communication to British Cardiac Society, London, May 26.
Turner, R. W. D. (1950). *Lancet*, **2**, 353.
—— (1951). *Practitioner*, **167**, 541.
—— (1959). *Lancet*, **1**, 897, 953.
—— and Lowther, C. P. (1959). Ibid., **1**, 769.

CEREBROSPINAL FLUID GAMMA-GLOBULIN IN MULTIPLE SCLEROSIS

OBSERVATIONS ON ITS NATURE

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It has been known for some time that the gamma-globulin level in the cerebrospinal fluid of cases of multiple sclerosis is commonly raised (Kabat, Moore, and Landow, 1942; Yahr, Goldensohn, and Kabat, 1954; Volk, Saifer, and Rabiner, 1954). It has been suggested that the rise may in part result from antibody formation within the central nervous system (Kabat, Moore, and Landow, 1942; Kabat, Freedman, Murray, and Knaub, 1950), though direct evidence of this is not available. The antiglobulin consumption test introduced by Steffen (1954) is capable of demonstrating increased globulin in the spinal fluid in multiple sclerosis, and in the present paper the ability of this excess globulin to fix to brain substrate has been examined.

Material and Methods

Spinal fluids of eight cases of acute exacerbation of multiple sclerosis and of 24 chronic cases have been tested.

A suitable specimen (clear of all blood) was diluted 1 in 16 times. Dilutions of a Coombs serum (final titre 1 in 2,048) from 1:16 to 1:512 were prepared and single drops plated out on to a clean glass plate. To each, one drop of the diluted spinal fluid was added. Interaction, aided by occasional gentle agitation, was allowed to take place for five minutes at room temperature. One drop of sensitized Group O Rh+ cells was then added to each mixture and any agglutination recorded at five and again at ten minutes. The globulins of the spinal fluid reacted with some of the Coombs reagent so that its original titre was reduced.

A suspension of normal human white matter was prepared by cutting frozen sections of the fresh tissue at 30 μ, and disrupting these in saline in a blender. The finely dispersed material was washed eight times to

remove all blood—so that the supernatant washing no longer reduced the titre of a Coombs serum with which it was mixed. The brain suspension was then made up to 20% v/v. Three drops of this suspension (from a standard-sized pipette) were put into a small tube, 20 drops of 1:16 C.S.F. added, and incubation was carried out in a water-bath at 38° C. for half an hour with occasional gentle agitation. This gave an opportunity for any antibody to brain present in the spinal fluid to become fixed upon the brain substrate. The spinal fluid was then spun off and its power to reduce the titre of Coombs serum re-estimated as described above—that is, its remaining content of globulin after exhibition to brain was assessed. Any reduction would be attributable to globulin antibody having become sessile.

Similar experiments were also carried out with lyophilized normal brain (from same subject), 2 mg. of this material being substituted for the three drops of 20% brain suspension in such cases. In this way the slight dilution of spinal fluid by water content of the brain suspension was obviated. Results were identical in both cases.

The whole series of experiments was repeated with wet acute multiple sclerosis brain, since it was thought that this might provide a better substrate than the normal organ.

Results

None of the spinal fluids from the eight different patients with an acute exacerbation gave a positive result—that is, in no case could antibody capable of fixing to either normal or multiple sclerosis brain be demonstrated. The fluids from 24 chronic cases of multiple sclerosis in various stages of the disease were also tested, with negative results.

Experiments were carried out on batches of six sera, chronic and acute cases being included, together with a healthy normal control. The accompanying table is the protocol of one such experiment, in which, as it happens, one normal control (B.V.) was examined at the same time as one acute case (P.T.) and four chronic cases. The failure of demonstrable absorption of any antibody upon the brain substrate, as shown by the absence of any significant difference between Coombs serum titre before and after exposure to it, is typical of all the results.

Typical Protocol of an Experiment Involving Six C.S.F. Specimens Showing Coombs Serum Titre Before and After Exposure to Brain Which had Been Incubated with the C.S.F. Under Examination. Eight Times Washed Normal Brain Used as Substrate

Patient		C.S.F. Dilutions					
		16	32	64	128	256	512
B.V. (normal control)	Before	+	+	+	+	+	±
	After	+	+	+	+	+	±
R.F.	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0
P.T. (acute)	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0
S.F.	Before	+	+	+	+	0	0
	After	+	+	+	+	±	0
E.C.	Before	+	+	+	+	0	0
	After	+	+	+	+	0	0
E.M.	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0

Patient S.F. showed a half-step decrease in titre. This is regarded as being within the limits of experimental error.

Readings of the completed agglutination at 10 minutes only are shown.

Discussion

These results suggest that the considerable increase in gamma-globulin known to occur in many cases of multiple sclerosis is not due in any large measure to antibody capable of becoming sessile upon normal brain substance under the conditions of the experiment. It is of course possible that only a small proportion of the gamma-globulin is in fact antibody, and an attempt was therefore made to set some limit to the sensitivity of the method in detecting globulin concentration changes.

1:16 dilutions of spinal fluids of known globulin concentration were titrated out as above. The lowest difference in concentration which could be detected (by difference in Coombs serum consumed) was estimated at 0.225 mg./100 ml., corresponding to 3.6 mg./100 ml., in the undiluted spinal fluid. Applying this figure to patient E.M., whose spinal fluid contained 50.5 mg. of gamma-globulin per 100 ml., but showed no antibodies capable of fixation to brain, it would seem that not more than 7% of his spinal-fluid globulin was antibody (as judged by the experimental criterion employed). It may, of course, have been a good deal less, or even nil.

The idea that a rise in the level of gamma-globulins in the spinal fluid is associated with the presence of antibody has an attractiveness which may be beguiling and deserves close examination, since it may colour thinking in respect to pathogenesis. Its immediate appeal derives from the presumed parallelism between the mechanism of multiple sclerosis and experimental allergic encephalitis in which some fraction or fractions of normal brain are known to be antigenic. On this basis the disease might be regarded as an autoimmune condition with the expectation of antibodies to brain in blood and cerebrospinal fluid—the situation being analogous to that in Hashimoto's disease. With the use of thyroid as a substrate there is no difficulty in demonstrating antibodies capable of becoming fixed in the serum of a high proportion of cases of Hashimoto's disease (Field and Ridley, 1960). While Steffen (1955) has successfully shown antibodies in the serum of multiple sclerosis cases, the titres he has found are far weaker than in Hashimoto's disease. Moreover, we have not so far been able to confirm Steffen's finding, and it seems reasonable to suppose that any antibodies present are of weak concentration and far less readily demonstrable than in a well-authenticated autoimmune condition such as Hashimoto's disease.

In interpreting the rise in gamma-globulin in the cerebrospinal fluid in multiple sclerosis, semantic equivalence between "gamma-globulin" and "antibody" must be avoided. "Whether all gamma-globulins are actually antibodies cannot be resolved at the moment," for "the amount of gamma-globulin readily accounted for by the more easily measured antibodies represents only a small fraction of the total gamma-globulin in adult human plasma" (Gitlin, Gross, and Janeway, 1959). The same caution in interpretation should apply to cerebrospinal fluid gamma-globulin. The present experiments suggest that there is no great local formation of antibody to brain tissue. The excessive gamma-globulin which is commonly (though not always) present might be (*a*) antibody to some other antigen—for example, virus or other infective agent such as a spirochaete—or (*b*) not of the nature of antibody at all.

As to the former possibility we have no evidence save that of Roach, Rosenberg, and Ichelson (1959), who

claimed to have found antibody to spirochaete antigen in the spinal fluid in multiple sclerosis. This claim has not been substantiated so far.

If the globulin (including gamma) rise in spinal fluid is not predominantly antibody, it may come from the disintegration of nervous tissue. This possibility was examined in the careful study by Yahr *et al.* (1954), who found that 35 cases of advanced amyotrophic lateral sclerosis, Friedreich's ataxia, poliomyelitis, syringomyelia, olivo-ponto-cerebellar degeneration, and combined system disease, all had gamma-globulin percentages within the normal range. From this they concluded that "destruction of neuronal tissue alone does not necessarily cause alteration in cerebrospinal fluid gamma-globulin content" (p. 662). However, the concentration in spinal fluid of any product of nervous-tissue disintegration must depend upon several factors, by no means all of which can be assessed. The degree of tissue destruction, the time over which it takes place, and the balance between liberation and resorption into the blood are perhaps the most obvious. It may be also that the clearance from the spinal subarachnoid space is less efficient in older and/or diseased subjects. Histological examination of active cases of multiple sclerosis will often show widespread disintegration of nervous tissue the total bulk of which appears much greater than in many advanced cases of the other diseases cited above. However, in the absence of quantitative data, the relative amounts of tissue destruction in these different conditions must remain an open question.

Direct evidence of the electrokinetic character of the protein material liberated when normal brain undergoes disintegration has become available (Hofmann and Schinko, 1956). This shows that about 19% alpha globulin, 54% beta-globulin, and 23% gamma-globulin are liberated from white matter. From cortex the percentages are 12, 67, and 19 respectively. It can be seen, therefore, that brain disintegration will make available for eventual passage into the spinal fluid considerable amounts of globulins, especially that characterized electrokinetically as beta. Whether breakdown along the lines which takes place in multiple sclerosis would result in a different spectrum of liberated protein is not known, but it does seem possible that under certain conditions the electrokinetically slower gamma fraction might be liberated in larger proportion. Concentration of different fractions (if indeed they exist as entities *in vivo*) must depend also upon the relative ease with which they are able to leave the subarachnoid space. The position is still further complicated by the fact that specimens of spinal fluid are nearly always taken from the lumbar cul-de-sac—a region far from the periventricular zone where lesions of multiple sclerosis tend to be greatest—so that opportunity exists for chemical modification of the fluid to be brought about before it is sampled.

In view of the multiplicity of uncontrolled factors it seems not unreasonable to entertain the hypothesis that the protein changes in spinal fluid may be secondary to nervous-tissue disintegration taking place under the spatial and temporal conditions peculiar to multiple sclerosis. There is general agreement that the greatest and most consistent elevations of gamma-globulins are found in long-standing cases of multiple sclerosis. It is difficult to reconcile an active pathogenetic significance of this with the burned-out picture which such cases present. On the other hand, it is consistent with derivation from destroyed nervous tissue with differential alteration in electrokinetic protein spectrum.

The presence or otherwise of antibodies to brain in spinal fluid has obvious significance for the formulation of a heuristic approach to the disease. So long as it is tacitly assumed that the frequent presence of gamma-globulin excess in spinal fluid indicates local brain antibody formation, the disease is likely to be regarded primarily as of an immune character. Liberation from such a shackling notion might stimulate effort in other directions.

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REFERENCES

Field, E. J., and Ridley, A. (1960). In press.
Gitlin, D., Gross, P. A. M., and Janeway, C. A. (1959). *New Engl. J. Med.*, **260**, 23.
Hofmann, G., and Schinko, H. (1956). *Klin. Wschr.*, **34**, 86.
Kabat, E. A., Freedman, D. A., Murray, J. P., and Knaub, V. (1950). *Amer. J. med. Sci.*, **219**, 55.
—— Moore, D. H., and Landow, H. (1942). *J. clin. Invest.*, **21**, 571.
Roach, L. L., jun., Rosenberg, S., and Ichelson, R. R. (1959). *Amer. J. med. Sci.*, **237**, 8.
Steffen, C. (1954). *Wien. Z. inn. Med.*, **35**, 422.
—— (1955). *Wein. klin. Wschr.*, **67**, 763.
Volk, B. W., Saifer, A., and Rabiner, A. M. (1954). *Ann. N.Y. Acad. Sci.*, **58**, 602.
Yahr, M. D., Goldensohn, S. S., and Kabat, E. A. (1954). Ibid., **58**, 613.

TRICHOPHYTON SULPHUREUM IN A RESIDENTIAL SCHOOL

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Trichophyton sulphureum has been recovered from humans in many parts of the world, but is an important cause of ringworm in only a small number of geographically limited areas. In Northern Ireland it is the most common cause of scalp ringworm among children (Beare, 1958), in contrast to other parts of Britain and Western Europe, where species of *Microsporum* tend to predominate. The lesions produced by *T. sulphureum* range from a mild, scarcely perceptible scaling or erythema to a relatively severe inflammatory and suppurative reaction (kerion) which may result in atrophy or scarring. Infection may persist for years, and the difficulty of clinical detection and the absence of Wood's light fluorescence of infected hairs make eradication of an outbreak in an institution "practically impossible" (Meenan, 1955).

In May and June, 1959, seven children from a Belfast residential school were found to be infected with *T. sulphureum*—three had infections of the glabrous skin and four had scalp infections. At this stage it seemed probable that the number of infected children in the school was higher than the seven known to be infected, and an attempt was accordingly made to determine the total number of infected children in the school, and to

eradicate the infection. At the same time investigations were made to elucidate the natural history of *T. sulphureum*. It was thought that repeated isolation of the pathogen from one or several sources would give a measure of the amount of infection in the school and indicate possible means of transmission.

School

At the time of the study there were 128 girls in the school, their ages ranging from 2 to 18 years. The dormitories and other accommodation were clean, bright, and well-ventilated.

Two previous outbreaks of ringworm infection were known to have occurred in this school. Walby (1952) reported an outbreak of *M. audouini*, which occurred in 1950, and in the course of his investigation a single *T. sulphureum* scalp infection was found. The infected child had been epilated by *x* rays and was still resident in the school, but free from infection, at the time of our investigation nine years later. In 1955 five children from this school were found to have *T. sulphureum* infection of the scalp. Two of them were still resident at the school. One child who had been treated with *x*-ray epilation showed no evidence of infection when re-examined four years later. The other, who originally had a very mild infection and had accordingly been treated with Whitfield's ointment, again showed on re-examination a mild lesion at the original site. It seems probable that this child had remained infective since 1955.

By sampling techniques described elsewhere (Mackenzie, 1960) it was found that *T. sulphureum* could be recovered from many non-living sites within the school, including hairbrushes and combs, and on the surface of pillow-slips. It was recovered from sites associated with children who were known to be infected, but it was also found on articles belonging to children who were ostensibly not infected. Other sites harbouring the fungus were floors, lockers, and a variety of bedding material. It was also demonstrated on three separate occasions (by placing a slit sampler 3 feet (90 cm.) from an infected child's bed) that aerial spread of infective material occurred during bedmaking.

Clinical Aspects

Twenty children, representing 15.6% of the population of the school, were found to be infected with *T. sulphureum* as follows:

Tinea capitis	13
Tinea corporis	4
Tinea capitis and tinea corporis	2
Tinea capitis and tinea unguium ..	1

The clinical appearances were somewhat variable, but in none of the children was there a marked inflammatory response. This is in contrast to the observation made by Beare (1958) that 28% of scalp infections by this fungus are inflammatory. The lesions on the body were usually single, erythematous, circinate, without conspicuously raised margins, and without marked scaling in the initial stages. Scalp lesions showed little or no inflammation, and in most cases consisted of poorly defined localized seborrhoea-like scaly patches, usually with occasional broken hairs. In only one child could infection be recognized readily from its appearance, and in this case scaling, loss of hair, presence of hair stumps, and erythema were pronounced. In the majority of the infections, particularly those of the scalp, clinical detection was extremely difficult. It was found that mild scalp disorders resembling seborrhoeic dermatitis, pityriasis alba, or even dandruff were occasionally shown mycologically to be infections caused by *T. sulphureum*.

Treatment

After mycological confirmation of the infection griseofulvin was administered orally (one tablet, 250 mg., three times daily) for an average period of 10 weeks. Lesions were also treated topically by the daily application of a fungicidal ointment (" bynamid "). For periods up to three months after the start of treatment samples from lesions were removed weekly and examined for the presence of the fungus. From our previous experience with griseofulvin it was known that at least three successive negative microscopical examinations and cultures were required before treatment could be stopped, but in the present study it was found that this did not provide a sufficiently strict criterion for cure, and the number of negative cultures was extended to at least four. It was not uncommon to find a positive culture reappear after several negative cultures had been obtained, and in one child *T. sulphureum* was isolated 45 days after apparent clinical cure and a series of four negative cultures.

In general, clinical improvement was usually evident within two weeks of starting treatment, but this was dependent on the site of infection.

Body.—Lesions on the glabrous skin responded more quickly than on other sites, and within a month erythema and scaling were no longer visible, the only sign of infection being a follicular plugging, which is discussed later. Resolution of the lesion did not imply simultaneous absence of infection, for, as already noted, the fungus could be demonstrated by microscopy and culture up to four weeks after an apparent clinical cure had been affected. In one child positive cultures were obtained after 8 to 11 weeks' treatment, when the original lesion was represented by a few " plugged " hair follicles.

Nail.—One child had an infection of her left index fingernail extending to the base of the nail. This cleared rapidly, and the nail appeared normal after 10 weeks' treatment. Cultures remained positive until the discoloured and dystrophic portion had disappeared.

Scalp.—Response to griseofulvin therapy was less marked and lesions tended to persist even when the fungus was shown by microscopy and culture to be absent. Hairs were occasionally shown to harbour *T. sulphureum* up to 13 weeks after the child's initial examination, but the first negative culture usually appeared after three to seven weeks. In one child a single positive culture was obtained after 12½ weeks of uninterrupted therapy, following a five-week period during which only negative cultures were obtained. At this stage broken hairs were still present within a small, pink, bald area which showed no scaling. Protection of the hair against the fungus became evident microscopically during the second week of treatment, when the intrapilar hyphae became displaced distally by the griseofulvin-protected hair. Microscopical examination, however, occasionally revealed the presence of arthrospores towards the base of hairs which were apparently normal but had not incorporated enough griseofulvin to displace the pathogen outwards. In another child a small number of arthrospores were observed outside the hair between the hair surface and the cells of the inner root-sheath. Both these children

had received up to eight weeks' treatment with griseofulvin combined with local application of bynamid, and, while this provided adequate control of most infections, it is clear that less strict criteria could result in a claim for "cure" although the fungus, as revealed by microscopy and recovery in culture, was still present and viable. Further examinations failed to reveal relapse of any of these lesions.

No new lesions were observed after the initiation of treatment, either in this investigation or in any other patient with ringworm whom we have examined.

Other Control Measures

In addition to examination and treatment of those infected, all other children were examined at regular intervals, and material from suspect lesions was examined in the laboratory. Non-infected children received griseofulvin prophylactically by oral administration at a reduced single dose of 50 mg. (one-fifteenth of the therapeutic dose) a day, in the form of tablets or a medicated syrup.

All sources shown by the mycological sampling techniques to harbour *T. sulphureum* were sterilized: articles of clothing and bedding were autoclaved and floors were washed with a proprietary coal-tar disinfectant. The compartments where hairbrushes were kept were washed with the same solution, dried, and repainted. Eventually all hairbrushes were renewed.

Results

After the eradication campaign periodic visits were made to the school to detect possible reappearance of infection on sites previously known to be infected. Follow-up clinical and mycological examinations were done at three- and six-month intervals after all children were apparently free from infection.

At the three-month follow-up examination all children were examined clinically and scales or hairs from suspect lesions were examined for the presence of fungi, but no signs of infection could be found. Mycological investigations at this time revealed that *T. sulphureum* was present in large numbers on one child's hairbrush and comb. Despite several rigorous searches of the child's scalp no infection could be found. The hairbrush was sterilized and returned on two occasions, replaced with a new brush on a third occasion, and examined at fortnightly intervals. Each time it was found to be infected. A hairbrush belonging to another child was later found to be infected, and *T. sulphureum* was isolated on three occasions from it before the child was ultimately discovered to have a scalp lesion. This was finally revealed at the six-month clinical follow-up examination, when three or four broken hairs from which the organism was grown were found at the scalp vertex. Scaling and redness were absent, and infection was detected only with great difficulty. This child has been isolated from the school and is being treated with griseofulvin, local application of a fungicide, and manual epilation of the infected hairs. On satisfying our criterion for cure she will be returned to the school and all the children will be examined once more; if no infection is found we may claim that eradication of *T. sulphureum* has been achieved.

The blood and urine of children receiving the therapeutic dose of griseofulvin were examined at the end of treatment. No abnormality was found.

Discussion

With the advent of griseofulvin dermatology has acquired a powerful new specific therapy against dermatophyte infections, and we believed that with its aid it might be possible to eradicate *T. sulphureum* from this residential school. For several reasons it was not possible to carry out a carefully controlled trial, and the methods adopted had to be judged solely on whether they did or did not eliminate infection. Perhaps the most cogent reason was the exceptional difficulty in detecting infection. The number of children known to be infected rose gradually over a six-month period; we do not believe that serial detection of this kind provides an adequate basis for a controlled experiment. In exceptional cases eight or nine clinical examinations were carried out before infection could be found, and it was clear in advance that there would be great difficulty in following the course of infection and in determining cure.

Mycological findings provided information that was of direct importance in the campaign of detection and eradication, and consequently influenced the methods of control adopted. The significance of these findings in connexion with the natural history of the pathogen was twofold. Firstly, a reservoir of infection was shown to be present within the school, including appreciable quantities of infective material in extrahuman sources. Secondly, there existed both opportunities and mechanisms whereby transfer of the fungus from one individual to another could occur. The role of the inanimate sources in maintaining and disseminating infection is difficult to evaluate with certainty, but their importance may be connected with the establishment of a high infection potential, compensating in part for the comparatively low degree of infectivity which this organism appears to possess. The presence of a single positive culture from a child's pillow or comb may well be accidental, and cannot be regarded as surprising after the demonstration that the pathogen can be disseminated aerially. On the other hand, of the 12 children whose effects gave two positive cultures, infection was confirmed clinically and by culture in 10. When three or more positive cultures were obtained the child was almost invariably found to be infected. In practice it was easier to isolate the fungus from a child's pillow or hairbrush than from her scalp, and on no fewer than six occasions a child was shown to be clinically infected after her effects were shown to harbour the pathogen.

The host/parasite relationship in infected children approaches that existing between host and commensal. Symptoms are not absent but are nearly so, and this "minimal-symptom" condition can apparently persist unchanged over a number of years, with the individual acting as a carrier of infection.

We believe that the measures adopted in the treatment of infection led to the formation of a fungal residuum, associated with the appearance of follicular plugging. This plugging presumably arose by desquamation and extrusion of the root sheath and neighbouring epidermal cells, and was particularly evident on body lesions where small, hard, compact, conical aggregations could be seen at most of the hair follicles; these were more clearly revealed by scraping the area with a blunt scalpel. If present in sufficient quantity these aggregations imparted a rough appearance and touch to the surface of the lesion. As they were shed or were rubbed off their numbers diminished, but the organisms

could usually be isolated so long as they were present, presumably from viable spores or hyphal fragments within the "residuum cone." No evidence was seen of acquisition of resistance by the fungus to griseofulvin, but there is no evidence that this might not occur when the drug is used in prophylaxis at a low dosage.

Conclusions

Our investigations showed that the fungus had been present in the school for probably not less than four years before the investigations began. It seems certain that we were dealing with a build-up of infection over a number of years rather than an outbreak. Large quantities of viable fungus were demonstrated in non-living sites, and it is believed that these extrahuman sources were important in transmission of the organism, in addition to direct transfer. The methods of control adopted were only partially successful, since a scalp infection was found six months after all known cases were cured. In this child five previous clinical examinations had failed to reveal a lesion. The prophylactic dose of griseofulvin did not apparently control the fungus in this case.

Perhaps the greatest single factor which has prevented complete elimination of the pathogen is the inability to detect infection, particularly that of the scalp. In our opinion it is almost impossible to detect what is virtually a carrier phase, and we found it necessary to have recourse to indirect examination—that is, the use of mycological techniques—to detect the organism on non-living sites such as hairbrushes, combs, and pillows. Probably complete elimination of the fungus could be achieved only by administering the full therapeutic dosage of griseofulvin to all children, combining this with regular clinical and mycological examinations and efforts to eradicate all extraneous infection.

Without griseofulvin there is little doubt that infection could not be eliminated from the school. The combined use of griseofulvin, topical treatment, and the removal of extraneous infection should ensure ultimate success.

Summary

Twenty children at a residential school were found to be infected with *T. sulphureum*. Eradication was attempted by therapeutic and prophylactic use of griseofulvin and by sterilization of all sites shown to harbour the fungus. Follow-up of all children at six months showed that with the exception of one child all were free from infection. At this time the fungus could still be recovered from a few non-living sites. Failure to eliminate all infection is attributed to the difficulty of clinical detection.

We thank Miss M. McArdle, Mr. D. L. Corkin, Dr. I. McCaw, Dr. J. M. Beare, Dr. A. D. Campbell, Dr. Kathleen Corbett, and Mr. W. Robinson for their assistance in this study. Glaxo Laboratories Ltd. provided the griseofulvin for prophylaxis.

ADDENDUM.—Since this article was submitted for publication an additional scalp infection has been found, bringing the total number of infected children to 21. This child owned the hairbrush described in the text, on which infection was repeatedly demonstrated, but on whose person no traces of infection could be revealed when examined clinically on 10 previous occasions. Two or three isolated broken hairs were found, and one of these gave rise to *T. sulphureum*; apparently only one hair was infected. Results now show that when the fungus was isolated on three or more occasions from the effects of any one child, that child was invariably found to be infected. A measure of the value of indirect examination in infections of the scalp can be gained by the discovery of infected hairs on seven children *after* the presence of the fungus was revealed by mycological sampling of their hairbrushes, combs, or bedding.

References

Beare, J. M. (1958). *Mycopathologia (Den Haag)*, **9**, 65.
Mackenzie, D. W. R. (1960). "Isolation of *Trichophyton sulphureum* from Non-living Sites in a Residential School." To be published.
Meenan, F. O. C. (1955). *Irish J. med. Sci.*, p. 321.
Walby, A. L. (1952). *Brit. med. J.*, **1**, 1114.

CONTROL OF DEGREE OF OXYGENATION DURING TOTAL BODY PERFUSION

BY

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AND

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Davies and Brink (1942) described the use of the platinum electrode for the polarographic measurement of partial pressure of oxygen (pO_2), ascribing its first use to Danneel and Nanst in 1897. Clark *et al.* (1953) described a modified electrode which has been used by us since January, 1959, for the continuous monitoring of oxygen content of blood, leaving a Kay-Cross spinning-disk-type pump oxygenator. The electrode has been used in experimental animal work by Clark *et al.* (1958) and Rennie, Reeves, and Pappenheimer (1958), and in clinical and experimental investigations by Montgomery and Horwitz (1950), Nahas, Morgan, and Wood (1952), Severinghaus and Bradley (1958), Urbach and Noell (1958), and Johansen and Krog (1959).

It is our policy to attempt to maintain physiological conditions during total body perfusion: the patient's temperature at, or as near as possible to, 37° C., and the venous blood oxygen saturation near 70%. To do this latter the flow is selected after consideration of the patient's surface area and age, and the pathology of the heart lesion. In this present group of cases the flow has varied between 1.8 and 3.4 l./min./sq.m., with a mean of 2.4 l./min./sq.m. The partial pressure of oxygen in blood leaving the oxygenator is maintained between 100 and 140 mm. Hg (giving a theoretical value of haemoglobin oxygen saturation of 98%) by alteration of the rate of revolution of the spinning disks.

The polarograph electrode assembly (Fig. 1) consists of a shiny platinum button and a silver–silver chloride indifferent electrode bathed in a saturated solution of potassium chloride, all enclosed in a lucite cylinder closed at the top by a nylon cap and at the bottom by a membrane of polyethylene 0.001 in. thick. The membrane is freely permeable to oxygen but prevents contamination of the platinum surface by blood.

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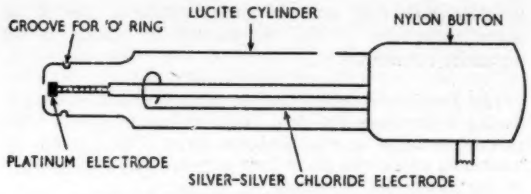

FIG. 1.—Diagram of the Clark electrode.

Oxygen is reduced at the platinum cathode (held at −0.6v in respect to the silver anode), causing the flow of a small current which can be measured by a sensitive galvanometer. The following equation represents the reaction:

$$O_2 + 4H^+ + 4(e) = 2H_2O$$

Sproule *et al.* (1957) have investigated the electrode and conclude that, within the physiological range its response to changes in partial pressure of oxygen is linear, that its temperature coefficient is linear, and that it is not sensitive to changes in *p*H, CO_2 concentration, or haematocrit. However, there are variations in the slope of the response curve from sample to sample, and because of this it is necessary to calibrate the instrument in the specimen of blood to be analysed.

The electrode is sterilized in formalin vapour before use, and is placed, enclosed in a suitable rubber stopper, in a port at the outflow end of the oxygenator (Fig. 2). The machine is primed with heparinized blood, the volume generally being between 3 and 4.5 l., and the polarograph is then calibrated. Calibration is performed by allowing the slowly recirculating blood to equilibrate—recognized by a steady state of the galvanometer—firstly with air (pO_2=140 mm. Hg) and then with carbogen (95% O_2+5% CO_2) (pO_2=680 mm. Hg), the corresponding galvanometer readings being noted.

If necessary they are adjusted to the same temperature by adding or subtracting 0.17 μA for each 1° C. temperature change, and then plotted on squared graph paper (Fig. 3). From this graph the galvanometer readings necessary to maintain a range of pO_2 100–140 mm. Hg are obtained, and during perfusion the pO_2 of the oxygenated blood can be immediately determined. The errors introduced by this method of calibration are small, as the priming volume is about equal to the patient's blood volume and the unexplained variations in slope tend to be minimized by the heterogeneity of the priming blood.

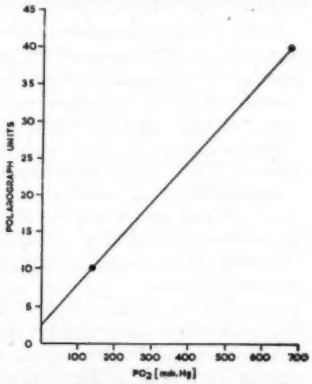

FIG. 3.—The calibration chart for the polarographg with the air and the carbogen points marked.

During perfusion, blood samples have been taken simultaneously from both arterial and venous lines and analysed for oxygen content and oxygen-carrying capacity (method of Van Slyke and Neill: Peters and Van Slyke, 1932), for haemoglobin content, and for *p*H and CO_2 content. In Fig. 4 are plotted the resultant arterial saturations against the graphically determined pO_2.

During the course of perfusion it is necessary to alter the disk-revolution rate quite often in order to maintain the desired range of pO_2. These changes are due to variations in both the quantity and the oxygen content of the venous blood returning to the oxygenator and of the cardiotomy return blood. In addition, we have found a variability in the amount and quality of the circulating haemoglobin. The measured haemoglobin oxygen-carrying capacity (method of Van Slyke and

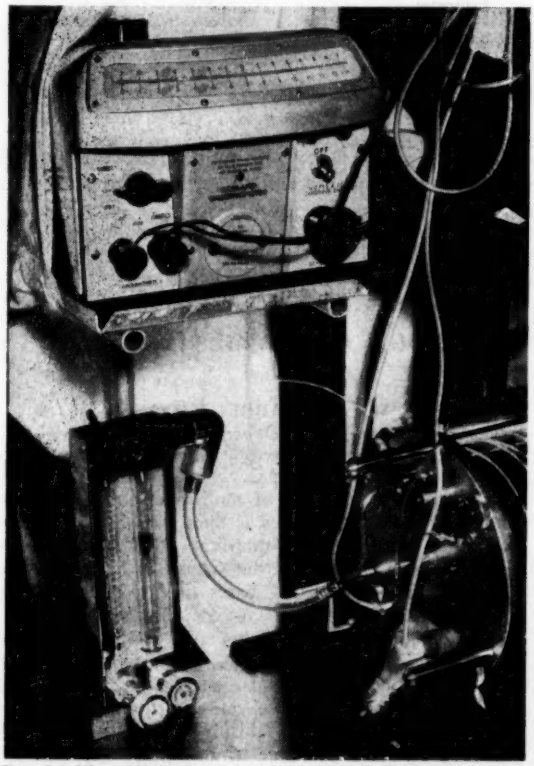

FIG. 2.—View of the arterial end of the Kay-Cross oxygenator with the Clark electrode in position. Also shown are the thermistor in the corresponding back port, the galvanometer, and the gas-flow meters for regulating the supply of carbogen and air to the oxygenator.

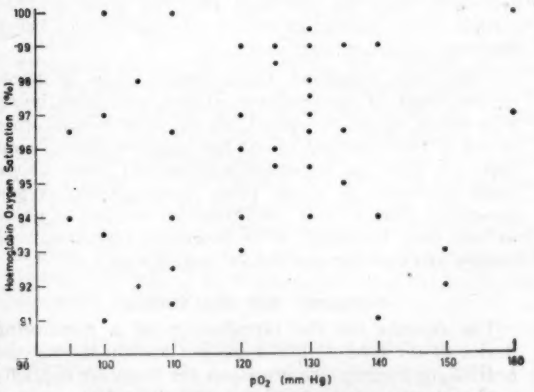

FIG. 4.—Plotting of arterial saturations against graphically determined partial pressure of oxygen (pO_2) of the last 26 perfusions. (Note (i) the range of the saturations; (ii) the apparent shift of the dissociation curve to the right.)

Neill) has been shown to be less than that calculated by the factor 1.34 c.cm. O_2/1 g. Hb, suggesting that the haemoglobin dissociation curve has been shifted "to the right." This is in direct contrast to the work of Valtis and Kennedy (1954), who demonstrated a shift to the left in stored blood, and of Van Slyke *et al.* (1946), who showed that "inactive" haemoglobin in freshly drawn blood disappeared after standing at room temperature for two hours.

Variables such as these cannot be predicted before the start of perfusion, and, once perfusion has begun, cannot be readily influenced. They are among the important limiting factors of the effectiveness of the perfusion.

While not firmly established, evidence is accumulating that high partial pressures of oxygen in arterial blood exert a deleterious effect on the function of cerebral tissues and to a less extent on other tissues. Dickens (1946) and Mann and Quastel (1946) have demonstrated a toxic effect on cerebral aerobic glycogen metabolism; Donald (1947) and Lambertsen *et al.* (1953a) showed a deterioration of cerebral function; and Lambertsen *et al.* (1953b) and Clark *et al.* (1953) showed an effect on cerebral blood-flow. Kirklin (1958) has indicated that this is the cause of otherwise unexplained post-perfusion deaths. All the evidence is derived from experiments in which a higher partial pressure of oxygen has been used than can be obtained in our machine, but Rennie and Pappenheimer (1958) have shown that, despite very high ambient pressures, the alveolar pO_2 always exceeds that of arterial blood.

In addition, there are the theoretical considerations of micro-bubble formation—discussed by Gibbon (1959)—and interference with carbon-dioxide transport (Peters and Van Slyke, 1931). We have found, too, that with disk speeds in excess of 130 there is a tendency for the blood to foam in the oxygenator and for small bubbles to appear in the blood leaving the oxygenator.

The undesirability of a low content of arterial blood oxygen, though not well documented, is generally accepted, leading, amongst other things, to a decrease in circulating blood *p*H and an increase in blood acidaemia (Biddulph *et al.*, 1958; Huckabee, 1958; and Magovern *et al.*, 1959). Tobian, Martin, and Eilers (1959) have shown that one of the effects of decreasing *p*H is to decrease the pressor action of noradrenaline.

If it is agreed that control of the degree of blood oxygenation leaving an artificial heart–lung machine is necessary, then we are sure that the polarographic method is the method of choice—the advantages being low cost, accuracy, and simplicity.

It has been suggested that oximetry could be used. In the range of haemoglobin oxygen saturation levels with which we are concerned, the oximeter is inaccurate owing to the flattening of the haemoglobin dissociation curve; it gives no information about pO_2 level above those necessary to cause 100% haemoglobin oxygen saturation (Nahas *et al.* (1952) has shown this to occur at 400 mm. Hg pO_2); it is expensive and cannot be readily adapted for continuous monitoring.

Summary and Conclusions

The reasons for the introduction of a monitoring device of the level of blood oxygen content leaving the heart–lung machine are discussed, the literature is briefly reviewed, the method of use of the Clark oxygen electrode is described, and some results are presented.

We would stress that the polarograph electrode circuit is simple and very reliable, the electrode is easily and quickly calibrated, and the pump operator can at all times determine if the oxygenator is acting as an adequate respirator.

The platinum oxygen electrode is as supplied by Yellow Spring Instruments Co. Inc., Yellow Springs, Ohio. The galvanometer is a Pye Scalamp Type 7904/3, and the associated circuit was made from standard radio components in our electronics workshop.

Our thanks are due to the help given by Mr. K. N. Morris, honorary thoracic surgeon to the Alfred Hospital, Melbourne, under whose direction this study was done.

References

Biddulph, Clyde, van Fossan, D. D., Criscuolo, D., and Clark, R. T. (1958). *J. appl. Physiol.*, **13**, 486.
Clark, L. C., Misrahy, G., and Fox, R. P. (1958). Ibid., **13**, 85.
—— Wolf, R., Granger, D., and Taylor, Z. (1953). Ibid., **6**, 189.
Davies, P. W., and Brink, F. (1942). *Rev. sci. Instrum.*, **13**, 524.
Dickens, F. (1946). *Biochem. J.*, **40**, 145.
Donald, K. W. (1947). *Brit. med. J.*, **1**, 667.
Gibbon, J. H. (1959). *Circulation*, **19**, 646.
Huckabee, W. E. (1958). *J. clin. Invest.*, **37**, 244.
Johansen, K., and Krog, J. (1959). *Acta physiol. scand.*, **46**, 228.
Kirklin, J. W. (1958). In *Extracorporeal Circulation*, edited by J. G. Allen. Thomas, Springfield.
Lambertsen, C. J., Kough, R. H., Cooper, D. Y., Emmel, G. L., Loeschcke, H. H., and Schmidt, C. F. (1953a). *J. appl. Physiol.*, **5**, 803.
—— —— —— —— —— —— (1953b). Ibid., **5**, 471.
Magovern, G. J., Cartwright, R. S., Neville, J. F., and Kent, E. M. (1959). *J. thorac. cardiovasc. Surg.*, **38**, 561.
Mann, P. J. G., and Quastel, J. H. (1946). *Biochem. J.*, **40**, 139.
Montgomery, H., and Horwitz, O. (1950). *J. clin. Invest.*, **29**, 1120.
Nahas, G. G., Morgan, E. H., and Wood, E. H. (1952). *J. appl. Physiol.*, **5**, 169.
Peters, J. P., and Van Slyke, D. D. (1931). *Quantitative Clinical Chemistry*, Vol. 1: *Interpretations*. Williams and Wilkins, Baltimore.
—— —— (1932). Ibid., Vol. 2: *Methods*. Williams and Wilkins, Baltimore.
Rennie, D. W., and Pappenheimer, J. R. (1958). *Proc. Soc. exp. Biol., N.Y.*, **99**, 515.
—— Reeves, R. B., and Pappenheimer, J. R. (1958). *Amer. J. Physiol.*, **195**, 120.
Severinghaus, J. W., and Bradley, A. F. (1958). *J. appl. Physiol.*, **13**, 515.
Sproule, B. J., Miller, W. F., Cushing, I. E., and Chapman, C. B. (1957). Ibid., **11**, 365.
Tobian, L., Martin, S., and Eilers, W. (1959). *Amer. J. Physiol.*, **196**, 998.
Urbach, F., and Noell, W. K. (1958). *J. appl. Physiol.*, **13**, 61.
Valtis, D. J., and Kennedy, A. C. (1954). *Lancet*, **1**, 119.
Van Slyke, D. D., Hiller, A., Weisiger, J. R., and Cruz, W. O. (1946). *J. biol. Chem.*, **166**, 121.

AETIOLOGY OF CONGENITAL TALIPES

BY

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The frequent occurrence of malformations in association with congenital talipes is well known. Attention has often been drawn to this fact. One of the more comprehensive reviews of the subject is by Ehrenfried (1912), who reviewed 232 cases of congenital talipes, with an incidence of associated anomalies of 13.4%. The anomalies included such conditions as congenital dislocation of the hip, mental deficiency, club-hand, cleft palate, amniotic bands, congenital herniae, and scoliosis. He ascribed the cause to heredity in those cases with a strong family history (about 10%), faulty nutrition of the zygote due to chorionic abnormalities, and mechanical distortion of the foetus.

Waller (1923) reviewed 735 cases of talipes and found a 4% incidence of associated anomalies. He reported that anomalies occurred twice as frequently in associa-

tion with talipes calcaneo-valgus as with talipes equino-varus. Keith (1940), in discussing "foetal dysplasia," described, amongst other foetal anomalies, cases with amniotic bands, intrauterine amputations, and talipes. He concluded that talipes was due to an area of mesenchymal dysplasia on the medial aspect of the foot, producing a cicatricial contracture which in turn produced the deformity.

Record and Edwards (1958), writing on the aetiology of congenital dislocation of the hip, reported an incidence of associated anomalies of 16%. The anomalies consisted of congenital herniae, hare-lip, spasticity, mental deficiency, and talipes (about 4%).

A similar review of sacral agenesis by Blumel, Burke Evans, and Eggers (1959) revealed anomalies ranging from arthrogryposis multiplex congenita to recto-vaginal fistulae in more than 90% of 50 patients exhibiting sacral agenesis. Congenital talipes occurred in 56% of these patients.

The present review was undertaken to ascertain the incidence of other congenital anomalies occurring in association with talipes in this clinic and to assess the significance of the findings in relation to the aetiology of congenital talipes.

Material

The report deals with 172 patients with congenital talipes attending the talipes clinic of this department and a review of the diseases occurring in the mothers of these children during the relevant pregnancy. All the patients are attending regularly and will continue to attend until maximum correction has been obtained and maintained. The methods of treatment follow the usually accepted principles of manipulation, splintage with Denis Browne splints, callipers, boots, and corrective surgery where indicated.

Of the 172 patients 40 (23.2%) have other congenital lesions (Table I). The anomalies (Table II) are of many varieties. Nine of the patients had siblings also included in the series, so the mothers numbered 167, all of whom were either interviewed personally or circularized. Of the 167 mothers 41 (25.1%) could not be interviewed or failed to return the circulars, but an accurate medical and family history was obtained from the remainder (126). Disease which may be significant occurred in 27 (21.4%); the diseases are tabulated in Table III.

Spence *et al.* (1954) quote an incidence of congenital anomalies of 1.5% in 1,142 infants. This figure represents the incidence of all major anomalies in a fairly representative selection of children in Newcastle upon Tyne, and corresponds fairly closely to the figure of 0.9% quoted by Fox *et al.* (1948) as being the incidence of all anomalies in the population as a whole. The anomalies occurring in Spence's survey are set out in Table IV.

TABLE I

Number of cases	172
C.T.E.V.	164
C.T.C.V.	8
C.T.E.V. with associated anomalies	40
C.T.C.V. " " "	0
Incidence of other anomalies	23·2%
Family history of talipes	12·8%

TABLE II.—40 *Associated Anomalies in this Series*

Congenital herniae	3
Spina bifida occulta	6
" " with neurological damage	2
Dysplasia of hip	1
Microcephaly	1
Arthrogryposis multiplex congenita	1
Spastic (one had pyloric stenosis)	3
Congenital dislocation of hip	2
Sacral agenesis	1
Multiple anomalies (see Table VI)	3
Arachnodactyly	1
Congenital absence of radius	1
Cleft palate and hare-lip	1
Mentally retarded	2
Achondroplasia	2
Growth defect lower tibial epiphysis (with short legs and varus deformity)	2
Torticollis	1
Pyloric stenosis (including one spastic)	3
Monostotic fibrous dysplasia	1
Amniotic bands on legs, with congenital amputation of toes	3
Webbed toes	1

TABLE III.—*Diseases Occurring in 27 Mothers During Pregnancy*

1. Toxaemia of pregnancy arising in the 3rd trimester of pregnancy; children had uncomplicated talipes	5
2. Hyperemesis gravidarum arising in the 1st trimester of pregnancy; 4 children had uncomplicated talipes, 1 child had amniotic bands and talipes	1
3. Mumps during the 1st trimester; child had achondroplasia	1
4. Anaemia, probably existed prior to pregnancy but treated during 2nd and 3rd trimesters; 4 children had uncomplicated talipes, 1 child had congenital absence of radius	5
5. Pulmonary tuberculosis diagnosed during 3rd trimester; children had uncomplicated talipes	2
6. Rubella occurring at 7 weeks; child had arachnodactyly and talipes	1
7. Congestive heart failure, probably arose during 2nd trimester; child had uncomplicated talipes	1
8. Diabetes mellitus (treated throughout pregnancy with insulin), also developed jaundice of unknown aetiology in 2nd trimester; child had uncomplicated talipes	1
9. Menstruation continued up to 6 months; child had uncomplicated talipes	1
10. Recurrent abortions; 1 child had talipes and torticollis, 1 child had uncomplicated talipes	2
11. Unknown eye lesion which necessitated many investigations, including lumbar puncture; child had uncomplicated talipes	1
12. Mother died in labour (thought to be due to a cardiac lesion); child had uncomplicated talipes	1
13. Generally unwell throughout pregnancy; child had uncomplicated talipes	1

TABLE IV.—17 *Anomalies Occurring in Spence's Survey*

Mongolian idiocy	4
Congenital heart disease (including 2 of the mongols)	4
Digital anomalies	4
Talipes	3
Spina bifida and hydrocephalus	1
Microcephaly	1
Cleft palate	1
Branchial cyst	1

Of the 40 patients showing other anomalies in the present series it was felt that many should be excluded from a statistical analysis. For example, the cases of pyloric stenosis, torticollis, and monostotic fibrous dysplasia are excluded as being of little or no significance in the present context. The six cases with spina bifida occulta are excluded because the incidence in the 40 patients (17.5%) is not in excess of the incidence (20%) one would expect in any 40 radiographs of the spine (Schinz *et al.*, 1952). A further eight cases, including the spastics, the patients with neurological damage secondary to spina bifida, the achondroplastics, and the patient with arthrogryposis, are excluded as the talipes in these patients is secondary to the major anomaly. The two patients with an abnormality of the lower tibial epiphysis are excluded because this condition may be the result of overenthusiastic manipulation, but it is strange that they are brother and sister.

The final selection of cases with associated anomalies is given in Table V; there are 20 cases, an incidence of 11.6%. Details of three cases with multiple anomalies are given in Table VI.

TABLE V.—20 *Severe Anomalies in Present Series*

Microcephaly	1	Congenital absence of radius	1
Congenital herniae	3	Cleft palate and hare-lip	1
" dislocation of hip	2	Amniotic bands	3
Sacral agenesis	1	Dysplasia of hip	1
Multiple anomalies (see Table VI)	3	Mentally retarded	2
Arachnodactyly	1	Webbed toes	1

TABLE VI.—*Three Cases Showing Multiple Anomalies in Present Series*

1. Klippel–Feil syndrome. Spina bifida and meningocele, C.D.H., and congenital scoliosis
2. Hemivertebra L5 and sacral anomaly; ventricular septal defect
3. Multiple upper-limb and chest anomalies; subsequently died at 8 weeks

Discussion

Browne (1936) evokes mechanical compression of the foetus as a factor in the production of such anomalies as talipes, spina bifida, congenital dislocation of the hip, and pseudarthrosis of the tibia. The evidence produced is certainly impressive and could account for the association of these conditions with talipes, but it could not account for the significantly high association of such anomalies as arachnodactyly, cleft palate, webbed toes, and sacral agenesis, which are probably faults in mesenchymal differentiation.

Heredity as a factor in the aetiology of talipes is accepted, but is operative in no more than 10% of all cases. It is felt that an incidence of other congenital anomalies of 11.6%, combined with the fact that the anticipated incidence of most of the anomalies found in this series is less than one per thousand, points to some common factor, or factors, in the production of talipes and other congenital anomalies. If the incidence of anomalies occurring in this series is compared with the incidence of congenital anomalies in Spence's review there is an 8 to 1 increase in the present series (Table VII).

TABLE VII

	Spence	Present Series	Total
Normal	1,125	152	1,277
Abnormal ..	17	20	37
Total	1,142	172	1,314

Fourfold table formula: $\frac{(19,916)^2 \times 1,314}{1,142 \times 172 \times 1,277 \times 37}$

$P<0{\cdot}01$; $\chi^2=56{\cdot}14$.

One of the arguments advanced against developmental arrest in the production of talipes is that the deformity is unlike any position normally adopted by the foetal foot. This is not in accordance with Keith (1948), who states that the foetal foot is inverted up to the seventh month of foetal life. This can readily be confirmed by observing the position of the feet in any aborted foetus. Further evidence of the existence of such a position in the developmental history of the foot is furnished by the alteration in the angle of the neck and distal articular facet of the talus between foetal and adult life (Wood-Jones, 1949). In addition, Böhm (1929) described several stages in early development (two to three months), during which the foot adopts positions of equinus, supination, and adduction.

If it is accepted that arrested development of the foot could produce the characteristic deformity of club-foot a search for the factors which might produce developmental arrest is necessary.

Warkany (1943, 1947) and Warkany *et al.* (1943) produced foot deformities in young rats by the production of deficiencies of vitamins A and D and riboflavine in pregnant rats. Duraiswami (1950, 1952, 1955) produced defects, including foot defects, in more than 70% of chick embryos by the injection of a variety of substances such as insulin, lead, and thallium nitrate into the yolk sac of fertilized hen's eggs. The interesting feature of the latter experiments was that it was found that there was an element of "time specificity" in that it was possible to reproduce consistently the same deformity according to the stage of development reached when the injection was made. For example, foot defects could be produced by insulin when the injection was made on the third day of incubation, whereas other defects, such as hip dislocation, could be produced by insulin injections made about the sixth day of incubation.

Similar results have been obtained with chick embryos inoculated with virus, although in these experiments early death of the embryo resulted and the malformations were very gross. The malformations in these experiments were largely restricted to the optic and otic capsules and the spinal column. Blattner and Williamson (1951) used Newcastle disease virus and Heath *et al.* (1956) used influenza, herpes simplex, and vaccinia virus in the production of the lesions.

Although it is dangerous to draw analogies between the production of experimental lesions in animals and the effects of disease in man, it seems reasonable to compare these experiments with congenital lesions in man known to be associated with interference in early development as a result of maternal infection and apparently similar lesions occurring in association with maternal disease such as diabetes mellitus. Gregg (1941) and Swan *et al.* (1943) drew attention to the association between congenital cataract and maternal rubella, and the occurrence of congenital defects of many types in association with maternal virus infections such as mumps has been reported by other observers (Fox *et al.*, 1948).

Maternal diabetes is known to be associated with a high incidence of abortion, and about 6% of children born of diabetic mothers exhibit various anomalies. In a review of 50 patients with sacral agenesis mentioned earlier, Blumel *et al.* record diabetes in 14% of the mothers. Only one mother with diabetes was found in the present series, but other conditions were also found to have existed during the relevant pregnancies. Some of these diseases, such as rubella and mumps, have been incriminated as aetiological factors in the production of congenital lesions, while others, such as hyperemesis gravidarum, pulmonary tuberculosis, congestive heart failure, and anaemia, have an unknown relationship to the production of congenital lesions.

It is impossible to draw any definite conclusions with regard to the part played by most of the maternal diseases mentioned in Table III in the aetiology of talipes, but it is felt that surveys conducted throughout pregnancy, rather than in retrospect, would prove helpful in indicating the underlying causative lesion in a high percentage of cases with congenital talipes.

Conclusions

The high incidence of other congenital anomalies occurring in association with talipes (11.6%) is thought to indicate a developmental aetiology in the production of talipes.

The incidence of maternal disease found in this series (21.4%) suggests that this is a factor of aetiological significance.

The final elucidation of the problem will require large-scale investigation of the diseases occurring during pregnancy and the correlation of the findings with the occurrence of congenital talipes.

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REFERENCES

Blattner, R. J., and Williamson, A. P. (1951). *Proc. Soc. exp. Biol. N.Y.*, **77**, 619.
Blumel, J., Burke Evans, E., and Eggers, G. N. (1959). *J. Bone Jt Surg.*, **41A**, 497.
Böhm, M. (1929). Ibid., **11**, 229.
Browne, D. (1936). *Proc. roy. Soc. Med.*, **29**, 1409.
Duraiswami, P. K. (1950). *Brit. med. J.*, **2**, 384.
—— (1952). *J. Bone Jt Surg.*, **34B**, 646.
—— (1955). Ibid., **37A**, 277.
Ehrenfried, A. (1912). *J. Amer. med. Ass.*, **59**, 1940.
Fox, M. J., Krumbiegel, E. R., and Teresi, J. L. (1948). *Lancet*, **1**, 746.
Gregg, N. McA. (1941). *Trans. Ophthal. Soc. Aust.*, **3**, 35.
Heath, H. D., Shear, H. H., Imagawa, D. T., Jones, M. H., and Adams, J. M. (1956). *Proc. Soc. exp. Biol. N.Y.*, **92**, 675.
Keith, A. (1940). *Brit. J. Surg.*, **28**, 173.
—— (1948). *Human Embryology and Morphology*, 6th ed. Arnold, London.
Record, R. G., and Edwards, J. H. (1958). *Brit. J. prev. soc. Med.*, **12**, 8.
Schinz, H. R., Baensch, W. E., Friedl, E., and Uehlinger, E. (1952). *Roentgen-diagnostics*, trans. J. T. Case, **2**, 1487. Grune and Stratton, New York.
Spence, J., Walton, W. S., Miller, F. J. W., and Court, S. D. M. (1954). *A Thousand Families in Newcastle upon Tyne*. Oxford Univ. Press, London.
Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B. (1943). *Med. J. Aust.*, **2**, 201.
Waller (1923). Quoted in Jones and Lovett's *Orthopaedic Surgery* (p. 578). Oxford Medical Publications.
Warkany, J. (1943). *Amer. J. Dis. Child.*, **66**, 511.
—— (1947). *Advanc. pediat.*, **2**. Interscience Publications, New York.
—— Nelson, R. C., and Schraffenberger, E. (1943). *J. Bone Jt Surg.*, **25**, 261.
Wood-Jones, F. (1949). In Buchanan's *Manual of Anatomy*, 8th ed., p. 47. Baillière, London.

HYPERNEPHROMA AND POLYCYTHAEMIA

BY

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The coexistence of hypernephroma and polycythaemia was reported for the first time in 1929 by Bliss, who described the presence of hypernephroma in a patient with polycythaemia as "an incidental complication."

The possibility of a direct causal relationship between hypernephroma and polycythaemia was suggested for the first time by Forssell (1946) and shortly after by Videbaek (1950). Both have described a case of hypernephroma with secondary polycythaemia which regressed after nephrectomy. Similar cases have subsequently been reported by Gros (1955), Conley *et al.* (1957), Damon *et al.* (1958), Campbell *et al.* (1958), Frey (1958), and Omland (1959).

Incidentally, the occurrence of hypernephroma and polycythaemia in the same patient is not particularly uncommon. The frequency of hypernephroma in patients with polycythaemia has been reported to be as follows: Videbaek (1950) found 2.4% in 125 patients, Lawrence (1955) 1.3% in 157 patients, and Damon and Holub (1958) 4.4% in 225 patients. The frequency of polycythaemia in patients with hypernephroma is, according to Damon *et al.* (1958), 2.6% (350 patients) and according to Berger and Sinkoff (1959) 1.8% (273 patients). A total of 41 cases of hypernephroma-polycythaemia have been reported in the accessible literature (Medvei, 1934; Fairley, 1945; Forssell, 1946, 1947, 1954, 1956, 1958; Lawrence, 1949; Videbaek, 1950; Stroebel *et al.*, 1951; Lawrence *et al.*, 1953; Gros, 1955; Moe, 1956; Herbeuval *et al.*, 1957; Sjöberg, 1957; Damon *et al.*, 1958; Frey, 1958; Lawrence and Donald, 1959; Omland, 1959), to which may be added a few cases stated to have been reported as "personal communications." An excellent review, adding also 10 new cases, was published by Damon *et al.* (1958).

Recently we had occasion to examine a case of coexisting hypernephroma and polycythaemia, which is reported in some detail below.

Case Report

A married farmer aged 60 was admitted to hospital on March 31, 1959. At the age of 16 he had scarlet fever, at 18 jaundice, at 22 "Spanish 'flu," and at 35 "gastric ulcer." For many years he had had a left-sided scrotal hernia. During the past 18 months he had been bothered by persistent pressure-pain below the left costal border; and during the past six months he had periodical haematuria, a tendency to sweat, and occasional oppression below the right costal margin. During the same period he had lost 10 kg. No headache, dizziness, or visual disturbances had occurred, no thrombotic episodes or haemorrhages apart from the haematuria, and no symptoms from other organs. Investigation about three weeks before admission had shown a haemoglobin level of 138–120%, R.B.C. 6,500,000/c.mm.; and W.B.C. 12,000/c.mm.

Findings on Examination

Polycythaemic facies; no dyspnoea at rest; no goitre or enlargement of lymph nodes; auscultation of lungs and heart showed no abnormality; spleen enlarged to the umbilicus; liver and kidneys impalpable; left-sided varicocele; prostate normal. Weight, 72.5 kg.; height, 172 cm.; blood-pressure, 140/85 to 125/75 mm. Hg.

Urine.—Protein, 1 plus to 0; no sugar or blood. Daily output, 470–1,020 ml. (specific gravity, 1016). Microscopical examination: 1 plus protein and 5–6 red cells when first studied; no abnormality the second time; no tumour cells on centrifugation, and no growth on culture.

Erythrocyte sedimentation rate, 3 mm./hour; Hb, 18.1 g./100 ml.; R.B.C., 6,580,000/c.mm.; colour index, 0.90; volume index, 1.00; W.B.C., 8,300/c.mm. (80% neutrophils, 3% eosinophils, 1% basophils, 9% lymphocytes, and 7% monocytes). Red blood picture normal. Platelets 260,000/c.mm.; prothrombin-proconvertin, 100%. The serological test for syphilis was negative. Blood group A Rhesus D negative (cde). Plasma volume, 3,750 ml. (determined with J-131-albumin (I.H.S.A., Amersham) by Dr. T. Munkner); haematocrit, 59 vols.%; total quantity of blood, 9,150 ml. (normal value for his height and weight, 4,900 ml.). Serum bilirubin, 0.9 mg./100 ml.; thymol, 0.03 unit, alkaline phosphatase, 16.4 units (normally 3–10 units); serum creatinine, 1.7–1.3 mg./100 ml.; serum calcium, 11 mg./100 ml.; serum phosphorus, 4.2 mg./100 ml.; serum uric acid, 6.4 mg./100 ml. Basal metabolic rate, +24%; pulse, 68. E.C.G.: left axis deviation, but no other abnormalities.

An intravenous pyelogram showed the right kidney to be normal, the left one somewhat elevated. The ureter was displaced slightly to the medial aspect. There was a suspicion of tumour of the left kidney. Retrograde left-sided pyelography revealed the ureter extending in an arch around a soft-tissue shadow in the left flank, and the pelvis situated at the upper pole of a mass extending to two centimetres distal to the iliac crest.

X-ray of chest: Heart normal. At the sternal end of the right first rib was a shadow, 3 by 1.5 cm., closely connected with the first rib. ?Ecchondroma.

Cystoscopy showed no abnormality.

Diagnosis: hypernephroma of left kidney, secondary polycythaemia.

Operation.—Left-sided nephrectomy was carried out on April 11 (Professor Dahl-Iversen). The tumour was 10 cm.

in diameter, situated in the lower half of the kidney and invading the renal pedicle, which was also removed. Two blood transfusions were given in the course of the operation and one during the first 24 hours after. The tumour tissue was yellowish, necrotic, and bleeding. Histological study (Dr. E. Badsberg): "tumour made up of clusters of fairly large cells with an ample, pale cytoplasm; the nuclei are roundish, fairly uniform, with ample chromatin and without mitoses; large parts of the tumour tissue necrotic, with scattered haemorrhages. Histological diagnosis: hypernephroma."

Blood study two weeks after the operation: Hb, 95%; R.B.C., 5,680,000/c.mm.; colour index, 0.81; W.B.C., 10,480/c.mm., with normal differential count.

Second Admission

Eight weeks after the operation the patient was readmitted because of anorexia, vomiting four to six times daily, and a loss of 3.5 kg. in the course of the past week. He was dehydrated and debilitated, and still had polycythaemic facies. The liver was enlarged to the umbilicus; the spleen was not palpable. There was resistance in the left flank. Lasègue's sign was positive at 70 degrees on the right.

Body weight, 65.2 kg. Blood-pressure, 125/85–120/65 mm. Hg. Urine negative for protein, sugar, and blood; daily output 520–1,420 ml. (specific gravity 1004). Microscopical examination: 3–6 leucocytes and 1–3 erythrocytes, but no other abnormalities. Culture of urine: A few *Staph. aureus* and diphtheroid rods of doubtful pathogenic significance.

E.S.R., 2 mm./hour; Hb, 15.9–14.7 g./100 ml.; R.B.C., 6,080,000/c.mm.; colour index, 0.84; haematocrit, 51 vols. %; reticulocytes, 18–16 per thousand; platelets, 335,000/c.mm. Serum bilirubin, 1.2 mg./100 ml.; alkaline phosphatase, 26 units; serum sodium, potassium, and chloride, normal. Standard bicarbonate, 27.4 mEq/l.; serum creatinine, 2.2–1.9 mg./100 ml.; serum uric acid, 10.9 mg./100 ml. Serum electrophoresis: total protein, 6.7 g./100 ml.; reduced albumin fraction (3.13 g./100 ml.) and increased gamma-globulin (1.30 g./100 ml.).

Radiographs of stomach: No abnormalities.

Radiographs of chest: In both lung fields there were diffuse minor infiltrations as well as several large, more well-defined ones. The previously mentioned ecchondroma had increased in size and was now clearly seen to be a lung tumour. Diagnosis: pulmonary metastases.

The patient died at the local hospital on July 10, 1959 (13 weeks after the nephrectomy). Hb level just before death, 85%. Necropsy was not performed.

Discussion

This case fulfils the demands of Damon *et al.* (1958) for a diagnosis of polycythaemia—namely, a haemoglobin level exceeding 18 g./100 ml., red-cell count exceeding 6,300,000/c.mm., and a haematocrit value exceeding 55%. The presence of a real polycythaemia was further confirmed by determination of the blood volume. The white-cell and platelet counts were normal, as is usual in patients with the hypernephroma-polycythaemia syndrome (pointed out among others by Damon and associates, 1958). Thus, as a rule there is a question of polyglobulism, not of a myeloproliferative syndrome. Oxygen saturation and pCO_2 determination on arterial blood were not done, but the studies of the lungs and heart did not show any evidence of lung or heart disease involving secondary polycythaemia. There were no signs of Cushing's disease.

The microscopical appearance of the tumour of the left kidney was typical of hypernephroma. The haemoglobin, erythrocyte, and haematocrit values became normal after the operation despite the presence of metastases at that time. However, the follow-up period is too short to draw any conclusions on this basis. These blood values may also become normal in patients with polycythaemia after any form of surgery, as pointed out among others by Videbaek (1950). However, the case-history and the objective findings seem to justify the assumption that this was a case of hypernephroma and secondary polycythaemia.

The association of hypernephroma and polycythaemia might be interpreted as occurring by chance. With the evidence at hand, this possibility cannot be definitely ruled out, but the previously reported cases in which polycythaemia has regressed after nephrectomy certainly support the assumption that hypernephroma may give rise to polycythaemia.

Nephrogenous polycythaemia may be observed not only in cases of hypernephroma. Forssell (1958) saw four cases of polycythaemia in patients with polycystic kidneys. Cooper and Tuttle (1957) were the first to describe a case of erythrocytosis in a patient with hydronephrosis. Lawrence in 1954 (cited by Forssell, 1958) reported a case of polycythaemia in a patient with renal fibromyxoma, and DeMarsh and Warmington (1955) described a case with renal adenoma and polycythaemia. Jones *et al.* (1960) have published a detailed report of polycythaemia in 10 cases of non-neoplastic renal diseases. In several of these cases the polycythaemia subsided after nephrectomy. These cases lend further support to the theory that the kidney may be an aetiological factor in certain forms of polycythaemia.

But what is the pathogenesis of nephrogenous polycythaemia? As demonstrated by Lawrence (1955), among others, the polycythaemia in idiopathic as well as secondary cases is due to increased production of red cells. The stimulation of the erythropoietic tissues is presumably humoral. In normal human plasma, concentrated 10 times, Gurney *et al.* (1957) found an erythropoietic factor, erythropoietin. Contopoulos *et al.* (1957) and Linman and Bethell (1957) have demonstrated erythropoietin in plasma from polycythaemic patients. In rats and rabbits, erythropoietin—or a precursor thereof—is presumably formed in the kidney, as bilateral nephrectomy reduces these animals' ability to form erythropoietin, whereas excision of other organs, including 90% of the liver, has no influence upon this ability (Jacobson *et al.*, 1957). It cannot be ruled out entirely, however, that the kidney may activate a precursor of erythropoietin formed in some other site. It is reasonable to assume that approximately the same applies to man. Thus the erythropoietin is assumed to be formed in the kidney, to be released to the blood, and to give rise to increased erythropoiesis in the bone-marrow.

This leaves the question why the formation of erythropoietin is increased in certain cases of hypernephroma, and sometimes also in other renal disorders. It has been suggested that the stimulus is anoxia, believed, in patients with hypernephroma, to be due to an arteriovenous shunt in the usually vascular tumour tissue. In experiments in rabbits Erslev (1957) found that anoxia due to anaemia or hypoxaemia lasting for more than six hours gives rise to increased erythropoietic activity in the blood. Damon *et al.* (1958), determining the arterial oxygen saturation in four patients with hypernephroma-polycythaemia, found normal values. Since, however, their blood specimens were derived from arteries of the limbs, these findings do not rule out the possibility of local renal anoxia

acting as a stimulus of increased erythropoietin production.

Keller (1957) demonstrated that patients with polycythaemia form a special haemopoietin which, unlike normal haemopoietin, is inactive after oxidation. This inactivation is reversible, since the haemopoietin is reactivated after reduction (addition of ascorbic acid). This particular haemopoietin may be imagined to be formed in anoxic renal tissue.

Perhaps this oxygen-sensitive erythropoietin is formed in tumour tissue. Our patient—and a number of the previously reported patients with hypernephroma-polycythaemia—had metastases at the time when polycythaemia was diagnosed. In Omland's (1959) case the polycythaemia reappeared twice, simultaneously with the appearance of metastases, and on both occasions it regressed after radiotherapy to the metastases. This theory might perhaps explain why polycythaemia has been encountered also after other non-nephrogenous tumours, such as uterine fibromyoma, cerebellar haemangioblastoma, hepatoma, and metastatic carcinoma of the lung or prostate. The explanation why it is not more commonly associated with tumours might be that, owing to a toxic action, the bone-marrow fails to react to erythropoietin in many types of cancer. Keller (1957) found that in certain kidney diseases there is hardly any erythropoiesis—despite a high erythropoietin level in the blood—and his explanation is that the bone-marrow has been exposed to a toxic action. Thus, the pathogenesis of secondary polycythaemia is far from having been elucidated.

Which cases of polycythaemia, then, ought to be investigated particularly for underlying hypernephroma? In our case the sedimentation rate was 3 mm./hour on admission. This value is generally 0 or a maximum of 1 mm./hour in cases of polycythaemia. A sedimentation rate exceeding 1 mm./hour in a patient with polycythaemia ought to draw attention to the possibility of hypernephroma. In the present case haematuria was a predominant and very early sign. Videbaek (1950) found haematuria in 7% of 125 polycythaemic patients. Thus, haematuria in a case of polycythaemia is not tantamount to demonstrable disease of the urinary tract, especially hypernephroma. If a polycythaemic patient has a sedimentation rate exceeding 1 mm./hour, an attempt should be made to find its cause. The possibility of hypernephroma should be considered, particularly in the presence of haematuria or an elevated α_2 value in serum electrophoresis. If intravenous pyelography does not reveal signs of renal tumour, aortography is indicated to rule out hypernephroma, especially if the α_2 value alone is elevated in serum electrophoresis.

Summary

A case of metastatic hypernephroma and polycythaemia is described. Symptoms had been present for about 18 months. The diagnoses and their relationship are discussed. The patient died 13 weeks after nephrectomy of metastases in the lungs and liver, so that the effect of nephrectomy upon the polycythaemia could not be assessed.

Forty-one previously published cases of hypernephroma-polycythaemia are reviewed. Mention is made of nephrogenous polycythaemia due to causes other than hypernephroma. The most likely explanation of the increased erythropoiesis is believed to be erythropoietin. Various investigations into this subject are reviewed and the pathogenesis is discussed. In the presence of haematuria—combined with an erythrocyte sedimentation rate exceeding 1 mm./hour or an elevated α_2 value—in a polycythaemic patient, intravenous pyelography is always indicated.

REFERENCES

Berger, L., and Sinkoff, M. W. (1957). *Amer. J. Med.*, **22**, 791.
Bliss, T. L. (1929). *Ann. intern. Med.*, **2**, 1155.
Campbell, J. H., Pasquier, C. M., St. Martin, E. C., and Worley, P. C. (1958). *J. Urol. (Baltimore)*, **79**, 12.
Conley, C. L., Kowal, J., and D'Antonio, J. (1957). *Bull. Johns Hopk. Hosp.*, **101**, 63.
Contopoulos, A. N., Lawrence, J. H., McCombs, R. K., and Simpson, M. E. (1957). *Clin. Res. Proc.*, **5**, 30.
Cooper, W. M., and Tuttle, W. B. (1957). *Ann. intern. Med.*, **47**, 1008.
Damon, A., and Holub, D. A. (1958). Ibid., **49**, 43.
—— —— Melicow, M. M., and Uson, A. C. (1958). *Amer. J. Med.*, **25**, 182.
DeMarsh, Q. B., and Warmington, W. J. (1955). *Northw. Med. (Seattle)*, **54**, 976.
Erslev, A. J. (1957). *J. Lab. clin. Med.*, **50**, 543.
Fairley, K. D. (1945). *Roy. Melb. Hosp. clin. Rep.*, **16**, 47.
Forssell, J. (1946). *Nord. Med.*, **30**, 1415.
—— (1947). Ibid., **35**, 1479.
—— (1954). *Acta med. scand.*, **150**, 155.
—— (1956). *Nord. Med.*, **56**, 1660.
—— (1958). *Acta med. scand.*, **161**, 169.
Frey, W. G. (1958). *New Engl. J. Med.*, **258**, 842.
Gros, H. (1955). *Medizinische*, **1**, 706.
Gurney, C. W., Goldwasser, E., and Pan, C. (1957). *J. Lab. clin. Med.*, **50**, 534.
Herbeuval, R., Cuny, G., and Larcan, A. (1957). *Presse méd.*, **65**, 132.
Jacobson, L. O., Goldwasser, E., Fried, W., and Plzak, L. F. (1957). *Trans. Ass. Amer. Phycns.*, **70**, 305.
Jones, N. F., Payne, R. W., Hyde, R. D., and Prize, T. M. L. (1960). *Lancet*, **1**, 299.
Keller, H. M. (1957). *Proceedings of Sixth Congress of European Society of Haematology, Copenhagen*, p. 1054.
Lawrence, J. H. (1949). *J. Amer. med. Ass.*, **141**, 13.
—— (1955). *Polycythemia: Physiology, Diagnosis, and Treatment.* Grune and Stratton, New York.
—— Personal communication. Cited by Forssell (1958).
—— Berlin, N. I., and Huff, R. L. (1953). *Medicine (Baltimore)*, **32**, 323.
—— and Donald, W. G. (1959). *Amer. J. med. Sci.*, **237**, 488.
Linman, J. W., and Bethell, F. H. (1957). *J. Lab. clin. Med.*, **49**, 113.
Medvei, C. V. (1934). *Wien. Arch. inn. Med.*, **24**, 417.
Moe, E. (1956). *Nord. Med.*, **56**, 1164.
Omland, G. (1959). *Acta med. scand.*, **164**, 451.
Sjöberg, A. J. (1957). *Nord. Med.*, **57**, 294.
Stroebel, C. F., Hall, B. E., and Pease, G. L. (1951). *J. Amer. med. Ass.*, **146**, 1301.
Videbaek, Aa. (1950). *Acta med. scand.*, **138**, 179, 239.

Reading University has acquired the scientific library of the late Professor F. J. COLE, F.R.S., who was professor of zoology there from 1907 to 1939. The library consists of some 8,000 volumes on the history of zoology and was bequeathed by Professor Cole to Dr. N. B. EALES, who worked with him for many years as a member of his department. It forms a complement to the Cole Museum of Zoology, which is already housed in the zoology department. The library contains two incunabula—Pliny's *Natural History* (1472) with 37 illuminated initials, and Aristotle's *Book of Animals* (1476). There is one section missing from the latter, now represented by a photofacsimile. Among the sixteenth-century books are the first and second editions of Vesalius's *De humani corporis fabrica* (1543 and 1555), Estienne's *La dissection des parties du corps humain* (1546), and the second Giunta edition of Galen's *Omnia Opera* (1550). The seventeenth century is represented not only by many famous individual authors but also by complete series of rare publications of the learned societies of the period. The outstanding books of the eighteenth century include the works of Manget, Stubbs, Ruini, Ruysch, and the two Hunters. The collection will eventually be housed in the university's new library, which is at present being built in Whiteknights Park, and will occupy a special room to be known as the Cole Library. (*The Times*, August 27.)

SUCCESSFUL MAINTENANCE OF PERNICIOUS ANAEMIA PATIENTS WITH VITAMIN B_{12} AND INTRINSIC FACTOR FOR LONG PERIODS

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It is well established that many oral preparations of vitamin B_{12} and hog intrinsic factor (I.F.) cause haematological and clinical remission in pernicious anaemia (P.A.). Recent reports have claimed that these oral preparations have failed to maintain a satisfactory remission in a variable percentage of the P.A. patients (Blackburn *et al.*, 1955; Adams, 1957; Killander, 1957, 1958a, 1958b; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Bastrup-Madsen, 1957; Schwartz *et al.*, 1957, 1958; Berlin *et al.*, 1958a, 1958b; Pedersen and Ebbesen, 1958; Schwartz, 1958; Stokes and Pitney, 1958). The inability of these preparations to maintain the patients was judged by haematological indices (vitamin B_{12} serum levels, marrow examination, red blood cell count, and haemoglobin concentration) or by the measurement of the ability of the patients to absorb radioactive vitamin B_{12} when given I.F. Most of these studies on refractoriness have been conducted with preparations manufactured and available in Europe under the trade marks "bendogen," "cycloplex," and "bifacton."

In the present report, an extension of a preliminary report (Lichtman *et al.*, 1958; Williams, 1959), 24 patients were maintained on various commercial intrinsic factor preparations for 5 to 67 months without significant development of impaired absorption of vitamin B_{12}.

Materials and Method

Two different commercial preparations from the American Cyanamid Company were used. They are designated as WES 374 and WES 592. Each capsule of WES 374 contained 50 mg. of hog I.F. and 30 μg. of vitamin B_{12}, which was equivalent to 2 U.S.P. units† and each capsule of WES 592 contained 60 mg. of I.F. and 15 μg. of vitamin B_{12}, which was equivalent to 1 U.S.P. unit, since WES 592 was less potent than WES 374. The patients were maintained on 1 capsule per day of the particular preparation studied.

The urinary excretion test as described by Ellenbogen *et al.* (1955) and Ellenbogen and Williams (1958) was used to determine quantitatively the ability of the patients to absorb vitamin B_{12} with a standard I.F. preparation, 186–1. This preparation was previously studied by Baker and Mollin (1955), Callender and Evans (1955), Ellenbogen *et al.* (1955), Williams *et al.* (1956), and Ellenbogen and Williams (1958), and it was shown that 50 mg. of 186–1 was equivalent to the amount of intrinsic factor contained in 2–3 U.S.P. units.

All the urinary excretion tests in this report were conducted using 2 μg. (0.1–0.25 μc.) of vitamin B_{12} labelled with ^{56}Co, ^{58}Co, or ^{60}Co. The radioactivity of the urine specimens was determined with a specially designed beaker of 1-litre capacity adapted to fit over and around a NaI well-type scintillation crystal (Ellenbogen and Williams, 1956) or by counting 200 ml. in a highly efficient plastic-well scintillator slightly larger than described (Hine and Miller, 1956).

Results

The results of the urinary excretion test of the 24 patients in the present study, prior to any oral therapy, is given in Table I. The average excretion without intrinsic factor was 0.9% and with 50 mg. 186–1 was 10.5%. This is in excellent agreement with the value of 0.7 and 10.5% respectively in 128 P.A. patients not maintained on oral therapy and not included in this study. Nine

TABLE I.—*Urinary Excretion of Labelled Vitamin B_{12} in Pernicious Anaemia Patients With and Without Standard Intrinsic Factor* 186–1, *Prior to Oral Therapy*

Patient	Urinary Excretion Percentage of 2-μg. Oral Dose Excreted in 48 Hours	
	Without I.F.	With 50 mg. 186–1
1	0·9	9·9
2	0·4	—
3	0·1	12·9
4	0·5	19·2
5	0·6	4·2
6	1·0	6·1 (24-hour excretion)
7	1·5	15·3
8	1·6	12·1
9	1·0	3·9
10	2·3	17·5
11	—	—
12	0·3	16·2
13	1·1	6·6
14	0·4	10·5
15	0·5	8·8
16	1·4	13·8
17	0·2	—
18	0·5	7·5
19	0·3	6·8
20	0·1	5·7; 8·6
21	—	—
22	1·3	10·6
23	2·7	7·8
24	0	16·5
Averages	0·9	10·5

TABLE II.—*Urinary Excretion Tests on P.A. Patients on Oral Maintenance (Intrinsic Factor Concentrate WES 374 plus Vitamin B_{12})*

Patients	Period on Previous Oral Maintenance	Period of This Study	Urinary Excretion (%) with WES 374 and 2 μg. Vitamin B_{12}
1	14 months	11 months	11·9
2	4 ,,	17 ,,	12·4
3	8 ,,	14 ,,	7·7
4	10 ,,	18 ,,	10·1
5	16 ,,	12 ,,	15·2
6	15 ,,	7 ,,	9 9
7	9 ,,	15 ,,	14·4
8	36 ,,	15 ,,	19·5
9	12 ,,	18 ,,	7·3
		Average	12·0

*Present address: University of Georgia, Athens, Georgia.

†The amount of vitamin B_{12}-I.F. preparation equivalent to 1 U.S.P. unit was determined by haematological assays in pernicious anaemia patients in relapse according to the requirements of the Anti-anemia Preparations Advisory Board of the *U.S. Pharmacopoeia*. The red-cell and reticulocyte responses were compared with the criteria established by the U.S.P. board. (The Fifth Announcement of the U.S.P. Anti-anemia Preparations Advisory Board, August 1, 1948, *J. Amer. pharm. Ass., pract. Pharm. Ed.*, 1948, 9, 660–669.)

patients (Nos. 1–9) after a variable period of oral maintenance on various intrinsic factor preparations and/or the multihaematinics containing intrinsic factor preparations were then started on maintenance for 7 to 18 months with I.F. preparation WES 374. After this period of oral therapy with WES 374 the urinary excretion test was performed on these nine patients with 100 mg. of I.F. WES 374. As can be seen from Table II, the patients all exhibited adequate excretion; the average excretion was 12.0%. No refractoriness was noted. The total period of oral therapy of these nine patients, taking into account the previous oral maintenance, varied from 21 to 51 months. Patient 8, who was maintained the longest on oral therapy, showed the best ability to absorb vitamin B_{12} with I.F. WES 374.

At the completion of the study with WES 374 these same nine patients were placed on oral maintenance with I.F. WES 592 for 13 to 20 months. In five of these nine patients, immediately before the start of therapy with WES 592, the urinary excretion test was performed with WES 592. In addition, four to seven months after the start and at the completion of the period of study, the urinary excretion test was repeated. The data from this experiment are given in Table III. Except for Patient 6, there was no indication

TABLE III.—*Urinary Excretion Tests on P.A. Patients on Oral Maintenance (Intrinsic Factor Concentrate WES 592 plus Vitamin B_{12})*

Patient	Period on Previous Oral Maintenance	Period of This Study	Urinary Excretion (%) with WES 592 and 2 µg. Vitamin B_{12}		
			Start	During	End
1	25 months	17 months	6·1	4·8	6·0
2	21 ,,	13 ,,			9·2
3	22 ,,	20 ,,		4·0	3·5
4	28 ,,	17 ,,	10·5	14·1	7·8
5	28 ,,	15 ,,	12·0		9·4
6	22 ,,	17 ,,	9·6	9·0	3·8
7	24 ,,	18 ,,		10·5	9·2
8	51 ,,	16 ,,	17·6	13·9	12·2
9	30 ,,	16 ,,			3·2*
		Averages	11·1	9·3	7·1

* Patient gave 3·9% with I.F.C. 186–1 on initial test prior to any oral therapy.

that the patients showed any significantly reduced ability to absorb vitamin B_{12} with I.F. WES 592. Patient 9 had a limited ability to absorb vitamin B_{12} with intrinsic factor prior to any oral therapy, and the inclusion of his excretion in the averages at the end of the test period as well as the reduced absorption exhibited by Patient 6 contributes to the lower overall average at the end of this study as compared with the average at the initiation of the study (7.1 *versus* 11.1%).

TABLE IV.—*Urinary Excretion Tests on P.A. Patients on Oral Maintenance (Intrinsic Factor Concentrate WES 592 plus Vitamin B_{12})*

Patient	Period on Previous Oral Maintenance	Period of This Study	Urinary Excretion (%) with WES 592 and 2 µg. Vitamin B_{12}		
			Start	During	End
10	0 months	19 months			8·8
11	34 ,,	17 ,,		12·4	9·4
12	0 ,,	14 ,,	11·6	15·5	11·7
13	30 ,,	14 ,,			10·3
14	0 ,,	15 ,,			16·2
15	34 ,,	17 ,,		8·3	6·2
16	0 ,,	5 ,,			9·2
17	32 ,,	19 ,,		10·2	5·2
18	0 ,,	5 ,,	10·1		12·9
19	0 ,,	14 ,,			7·3
20	0 ,,	15 ,,	8·0	6·1	5·0
21	17 ,,	13 ,,			8·7
22	0 ,,	7 ,,			8·0
23	28 ,,	17 ,,	12·5	13·9	12·8
24	0 ,,	11 ,,			10·0
		Averages	10·5	11·0	9·7

Fourteen additional patients not previously maintained on other intrinsic factor preparations and/or the multihaematinics containing intrinsic factor preparations were also placed on maintenance study with I.F. preparation WES 592 with urinary excretion tests performed at the start, four to seven months after, and at the completion of the maintenance period.

As can be seen from Table IV, the average excretion of these 14 patients at the end of the maintenance period did not differ significantly from that at the start of the maintenance period.

Discussion

The present investigation shows that development of resistance to intrinsic factor is not an inevitable occurrence of all hog intrinsic factor preparations after prolonged oral treatment in P.A. patients.

The failure of oral treatment has been attributed to the formation of antibodies to the hog proteins (Schwartz *et al.*, 1958). This is somewhat supported by the fact that vitamin B_{12} absorption is inhibited in P.A. patients not previously treated orally when given vitamin B_{12}, I.F., and serum of patients previously treated orally with I.F. (Schwartz, 1958). Furthermore, many of these resistant patients absorb vitamin B_{12} when it is given together with 50 ml. of normal human gastric juice. On the other hand, Berlin *et al.* (1958a, 1958b) have found that some P.A. patients who have developed a resistance to hog I.F. do not respond to 50 ml. of normal human gastric juice. No long-term studies have been conducted with P.A. patients to determine if they will develop resistance after maintenance with gastric juice for long periods. Intrinsic factor from the wild boar failed to affect the "blocked" absorption, whereas rat gastric juice was effective in re-establishing vitamin B_{12} absorption (Schwartz *et al.*, 1958).

If the immunity theory is correct, this would imply that I.F. or some other protein component of the impure preparations is absorbed. As yet no data have been presented on whether I.F. is or is not absorbed. Furthermore, if one accepts the immunity theory as the cause of the blockage of absorption, then it must be assumed that during the fractionation and preparation of the cyanamid intrinsic factors used in this investigation the protein components giving rise to antibody formation were eliminated. Since some very crude preparations have been reported not to cause the development of resistance (Schwartz *et al.*, 1958), an alternative explanation may be that some unknown factor present in these crude preparations prevents the development of resistance. In view of the variable effects of different intrinsic factor preparations, Killander (1958a, 1958b) also believes that the development of resistance depends on the method of their manufacture.

Relatively large doses (the amount of intrinsic factor contained in the equivalent of 10 U.S.P. units or more) have been reported to abolish the "blocked" absorption in the resistant patients (Berlin *et al.*, 1958b). A patient not included in the maintenance study and who never received any oral therapy was found to have an unusually high requirement for I.F. This patient failed to absorb vitamin B_{12} with 50 mg. of I.F. 186–1 and with 5 mg. of a more purified preparation (I.F. WES 727). However, 500 mg. of 186–1 and 50–100 mg. of WES 727 cause optimum absorption (Table V). This patient excreted 6.4 and 11.5% with 30 and 50 ml. respectively of fresh acid normal human

TABLE V.—*Unusually High Intrinsic Factor Requirement (Patient J. S.)**

Intrinsic Factor Source	Amount	Urinary Excretion (%)
None (B_{12} alone) ..	—	0·1, 0·2
186–I (crude) ..	50 mg.	2·9, 1·7, 0·9
	500 ,,	7·7
727 (purified) ..	5 ,,	0·2
	50 ,,	11·0
	100 ,,	19·0
Acid human gastric juice	30 ml.	6·4
	50 ,,	11·5

* We acknowledge the co-operation of Dr. Jerome Adesman, of Brooklyn Jewish Hospital, Brooklyn, N.Y., for permission to study this patient.

gastric juice. This, taken together with the fact that Patient 9 had a low excretion with I.F. prior to any oral therapy, emphasizes the importance of conducting control absorption studies on the same patients prior to oral therapy.

The 2 to 3 U.S.P. units used in the urinary excretion tests in the present report could not be classified as a large dose. In most of the reports describing refractoriness, doubling or tripling the dose was not adequate to restore absorption where absorption was blocked. The necessity for using an amount of intrinsic factor contained in 2 to 3 U.S.P. units in the urinary excretion test with 2 μg. of radio-labelled vitamin B_{12} has been pointed out in previous communications (Williams *et al.*, 1956; Ellenbogen and Williams, 1958). Furthermore, the same amount of I.F. was used in the urinary excretion test at the beginning of the maintenance study as at the completion of the study with I.F. WES 592.

There appears to be no outstanding explanation why only one patient (No. 6) out of 24 patients showed a reduction in absorption of vitamin B_{12}. She was an extremely uncooperative subject, but a repeat urinary excretion test gave the same result. Possibly some type of latent malabsorption was developing.

Summary

Nine P.A. patients maintained on different B_{12}-I.F. preparations for 5 to 36 months, and then for 7 to 18 months on a single vitamin B_{12}-I.F. preparation equivalent to 2 U.S.P. units, failed to develop any resistance to the later preparation.

Only one out of 24 patients showed any significant indication of reduced absorption after oral maintenance for from 5 to 20 months on a preparation equivalent to 1 U.S.P. unit.

One P.A. patient who had never received oral therapy required approximately 20 times the usual amount of I.F. for optimum vitamin B_{12} absorption.

It is concluded that some I.F. preparations can successfully maintain P.A. patients for long periods without showing impaired absorption of vitamin B_{12}.

REFERENCES

Adams, J. F. (1957). *Scot. med. J.*, **2**, 151.
Baker, S. J., and Mollin, D. L. (1955). *Brit. J. Haemat.*, **1**, 46.
Bastrup-Madsen, P. (1957). *Acta med. scand.*, **159**, 323.
Berlin, R., Berlin, H., Brante, G., and Sjöberg, S.-G. (1958a). Ibid., **161**, 143.
—— —— —— —— (1958b). Ibid., **162**, 317.
Blackburn, E. K., Cohen, H., and Wilson, G. M. (1955). *Brit. med. J.*, **2**, 461.
Callender, S. T., and Evans, J. R. (1955). *Clin. Sci.*, **14**, 295.
Ellenbogen, L., and Williams, W. L. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 617.
—— —— (1958). *Blood*, **13**, 582.
—— —— Rabiner, S. F., and Lichtman, H. C. (1955). *Proc. Soc. exp. Biol. (N.Y.)*, **89**, 357.
Hine, G. J., and Miller, A. (1956). *Nucleonics*, **14**, 78.
Killander, A. (1957). *Lancet*, **1**, 1041.
—— (1958a). *Acta med. scand.*, **160**, 339.
—— (1958b). *Acta Soc. Med. uppsallen.*, **63**, 1.
Kristensen, H. P., Lund, J., Soeborg Ohlsen, A., and Pedersen, J. (1957). *Lancet*, **1**, 1266.
Lichtman, H. D., Ellenbogen, L., and Williams, W. L. (1958). *Third Vitamin B_{12} Symposium*, New York Academy of Medicine. New York.
Lowenstein, L., Brunton, L., Shapiro, L., de Leeuw, N., and Dufresne, M. (1957). *Canad. med. Ass. J.*, **77**, 923.
Pedersen, J., and Ebbesen, I. (1958). *Acta med. scand.*, **161**, 413.
Schwartz, M. (1958). *Lancet*, **2**, 61.
—— Lous, P., and Meulengracht, E. (1957). Ibid., **1**, 751.
—— —— —— (1958). Ibid., **2**, 1200.
Stokes, J. B., and Pitney, W. R. (1958). *Brit. med. J.*, **1**, 322.
Williams, W. L. (1959). *Fed. Proc.*, **18**, 351.
—— Ellenbogen, L., Rabiner, S. F., and Lichtman, H. C. (1956). *J. Lab. clin. Med.*, **48**, 511.

Medical Memoranda

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma, or metastasizing non-chromaffin paraganglioma, is a rare tumour with a distinct histological and clinical picture. Smetana and Scott (1951) and Christopherson *et al.* (1952) have each recorded a small series of cases; another case was described by Randall and Walter (1954). A further case is reported below.

CASE REPORT

In November, 1953, a woman aged 20 was referred to the chest clinic from the mass radiography unit. She complained of cough and lassitude, and there was a family history of tuberculosis. Chest *x*-ray examination showed a partly calcified focus beyond the left hilum. Thereafter she was observed regularly. In September, 1954, a round focus was noted in the left lower lobe; shadows appeared later at the left base (Fig. 1), and in July, 1955, she was admitted to Bow Arrow Hospital under the care of Dr. Michael Gibson. She was Mantoux-positive, and was treated with streptomycin and isoniazid; but doubt was expressed about the nature of the lesion. She returned home, and in November, 1956, attended the chest clinic when eight months pregnant; round foci were present in both lower lobes, and she was admitted to Grove Park Hospital. She had now developed a firm, painless swelling 2 by 3 in. (5 by 7.5 cm.) in the left erector spinae muscle. She was delivered of a healthy child on January 9, 1957.

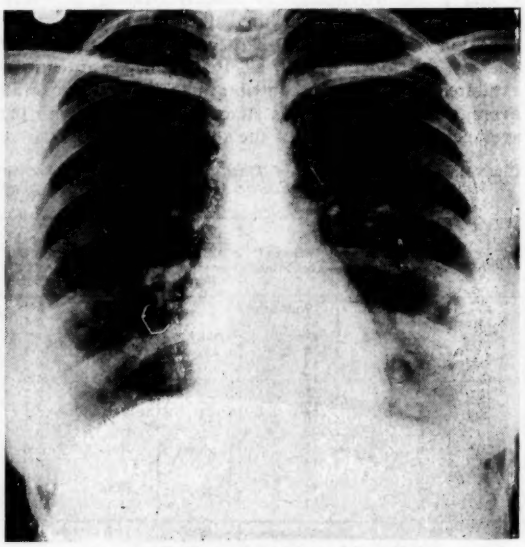

FIG. 1.—Radiograph of chest (May, 1955).

The tumour in her back was thought to be a hypernephroma, and an intravenous pyelogram was reported as diagnostic of this. Mr. A. Cavendish performed a retrograde pyelogram, which showed surprisingly little deformity of the pelvi-caliceal pattern. Mr. J. Jemson took a biopsy specimen from the muscle tumour, and Dr. M. O. Skelton gave the following report: "Section shows connective tissue invaded by epithelial cells showing in places a papillary arrangement, and in places as small groups of cells; in the light of the failure to demonstrate any renal neoplasm, I think this is a non-chromaffin paraganglioma, a so-called alveolar soft part sarcoma" (Fig. 2). Sections were sent to Professor W. M. Christopherson, of the University of Louisville, who commented on "the presence of very dense eosinophilic cytoplasm in many of the cells," and thought the tumour belonged to this group.

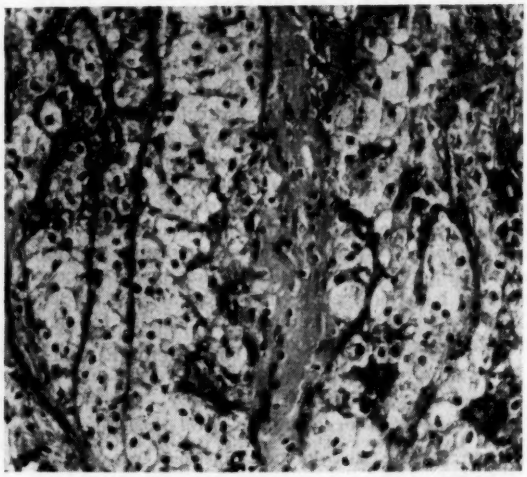

Fig. 2.—Section of muscle taken for biopsy. (×200.)

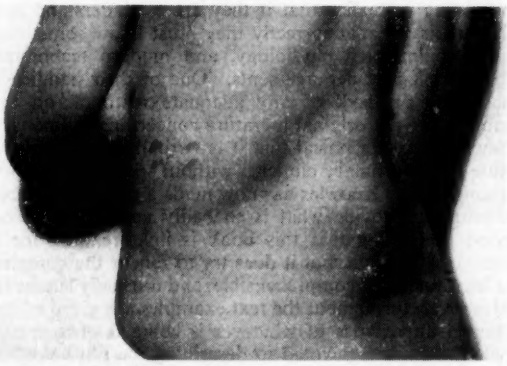

Fig. 3.—Muscle tumour in erector spinae (after biopsy).

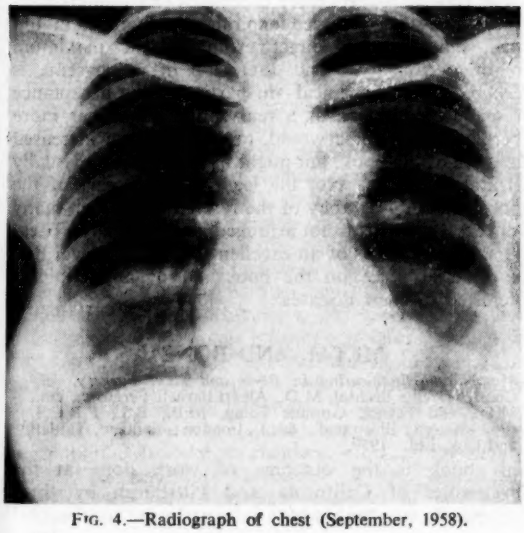

Fig. 4.—Radiograph of chest (September, 1958).

No further treatment was advised. The patient has continued her ordinary life and feels well. The mass in her back is unchanged (Fig. 3). Apart from several small haemoptyses and persistent amenorrhoea she remained well throughout 1958, but the pulmonary metastases have increased considerably (Fig. 4).

Comment

This tumour commonly presents as a slow-growing, painless mass developing in an extremity; usually it is encapsulated and located in a muscle or musculo-fascial plane. The majority of the patients have been young women; metastases are common and chiefly pulmonary. The prognosis is very variable; some patients have lived many years after excision of the primary tumour, and others with metastases have remained well for years. Treatment is surgical excision of the primary tumour; there has been no response to *x*-ray therapy; lobectomy has been performed occasionally for isolated pulmonary metastases.

Histologically there is a pseudo-alveolar arrangement of cells, the groups being separated by connective-tissue fibrils or vascular channels. The cells are polyhedral or oval with mildly acidophilic cytoplasm; the nuclei are large and vesicular. There is a vascular invasion by groups of cells, but this does not seem to bear on the prognosis. Primary and secondary tumours are histologically similar.

This tumour can be distinguished from renal carcinoma and from varieties of myosarcoma by the clinical course. The histogenesis is obscure; an origin from non-chromaffin paraganglionic tissue such as occurs in the carotid body (LeCompte, 1948) and retroperitoneal paraganglioma has been suggested, but Christopherson (1957, personal communication) is strongly opposed to this view. He considers the evidence for paraganglionic tissue in skeletal muscle rather nebulous; he prefers the non-committal term "alveolar soft part sarcoma."

I thank Dr. M. O. Skelton for the biopsy report and the photomicrograph.

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References

Christopherson, W. M., Foote, F. W., jun., and Stewart, F. W. (1952). *Cancer*, **5**, 100.
LeCompte, P. M. (1948). *Amer. J. Path.*, **24**, 305.
Randall, K. J., and Walter, J. B. (1954). *J. Path. Bact.*, **67**, 69.
Smetana, H. F., and Scott, W. F. (1951). *Milit. Surg.*, **109**, 330.

Samples of dust collected from the atmosphere at a height of about one metre above the ground at Chilton, Berkshire, show that radioactivity dropped to a very low level after nuclear test explosions were suspended. The monthly concentration of caesium-137 reached its highest peak of 10^{-13} μc/c.cm. in May, 1959. (*The Radioactivity of the Atmosphere Near Ground Level due to Distant Nuclear Test Explosions*, 1960, Health Physics Division, Atomic Energy Research Establishment, Harwell. H.M.S.O. Price 1s. 9d.)

Reviews

ANIMAL INFECTIONS

Infectious Diseases of Animals: Diseases Due to Bacteria. Edited by A. W. Stableforth, D.Sc., M.R.C.V.S., D.V.S.M., and I. A. Galloway, D.Sc., M.R.C.V.S. In two volumes. (Pp. Vol. I: 396+x; Vol. II: 397–810+x; illustrated. £8 per set.) London: Butterworths Scientific Publications. 1959.

These two important volumes are the work of 21 contributors. They are to be followed by another—or others—on rickettsial, virus, and protozoal diseases. They consist of 20 chapters, alphabetically arranged (actinomycosis to vibriosis), each dealing with disease due to a single species or genus of bacteria. A chapter on fungi is included. The chapters vary in length from 10 to over 100 pages, and most are remarkably comprehensive. Beginning with a detailed description of the micro-organism concerned, each deals with the morbid anatomy of the disease, its clinical features, its distribution and mode of transmission, and methods of diagnosis, prevention, and treatment. This combination of the laboratory and clinical outlook is admirable; the two are not wedded on such equal terms in any work which comes to mind in the field of medicine. Each chapter is fully documented; that on brucellosis by Stableforth concludes with 15 pages of references. The emphasis is naturally on animals of economic importance, with cattle in the forefront, but many other animals and birds are referred to where their susceptibility to a disease is of interest.

This is bound to become a standard work of reference for veterinarians, but some of those concerned with human disease will also be grateful for it. Of its 20 subjects 17 are diseases which have their counterpart in man, even though it may cause some surprise to suggest that foot rot in sheep and Vincent's infection of the human mouth have anything in common. Ten are diseases actually transmissible to man. Our profession is closely concerned in what is being done about tuberculosis and brucellosis in cattle, and we are entitled to be alarmed at the rising incidence of staphylococcal mastitis, and at the use not only of penicillin but even of chloramphenicol, dihydrostreptomycin, and corticosteroids in its treatment.

Chemotherapy does not appear to have been as well studied in the veterinary field as in the medical: trials are often reported in too few animals; cures are claimed by drugs which have no demonstrable action on the micro-organism; and antibiotics seem sometimes to fail where they should succeed. This may be because so much reliance is placed on local application, and, when systemic treatment is attempted, dosage and duration tend to be inadequate, perhaps because in a beast weighing half a ton the cost of adequate treatment would be prohibitive. This economic factor must be an obstacle to therapeutic research, and the ever-present alternative of slaughter also sharply distinguishes veterinary from medical practice.

Minor blemishes are the misspelling of names of drugs, and the use of obscure proprietary names, and of several ugly words—"hypocuprosis" for copper deficiency, an "adequately referenced account" (preface) and a disease (aspergillosis) "never adequately monographed." The work is handsomely produced—as indeed it should be at the price—and some chapters are liberally illustrated.

L. P. Garrod.

CEREBRAL DOMINANCE

Cerebral Dominance and its Relation to Psychological Function. By O. L. Zangwill, M.A. (Pp. 31+vii; illustrated. 10s. 6d.) Edinburgh and London: Oliver and Boyd for the William Ramsay Henderson Trust. 1960.

The phenomenon of cerebral dominance provides a puzzling challenge to all interested in the human brain. What can be the reason for the almost invariable fact that man uses his left cerebral hemisphere for speech? It had formerly been thought that this is related to being right-handed, but Professor Zangwill and others have shown that left-handers also generally use the left hemisphere for speech. There are indications, however, that some left-handers have a different way of using their brains and may even use both left and right sides equally; and in this connexion Professor Zangwill discusses possible psychological disadvantages of "cerebral ambilaterality." This is a very interesting suggestion which also raises the possibility that man's success in utilizing his brain may be due to, or at least be dependent on, his having acquired the capacity for having unilateral cerebral dominance.

W. Ritchie Russell.

LUNG FUNCTION

Respiratory Physiology and Its Clinical Application. By John H. Knowles, M.D. (Pp. 256+ix. 42s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959.

Chest physicians and surgeons in this country are beginning to realize that if they are to understand and treat their patients correctly they must know something about pulmonary physiology, and modern techniques for assessing its derangements. One of their handicaps has been the lack of any adequate textbook on the subject, for the original literature concerning pulmonary function is so technical that it is virtually incomprehensible to the ordinary clinician without special laboratory training. Dr. Knowles has now made a really admirable attempt to provide what is so badly needed. It is no good pretending that this book is light reading for a Sunday afternoon, but it does try to render the complex at least tolerably comprehensible, and it usually succeeds. Moreover, throughout the text examples are given of the clinical importance of whatever is being discussed, and half the book is devoted to describing the physiological derangements in a variety of diseases.

For English readers there is perhaps too little mention of the one-second forced expiratory volume, and too much emphasis on direct estimation of maximum breathing capacity. The discussion of emphysema is perhaps a little uncritical—in particular the acceptance of senile emphysema as a real entity. A rather more liberal use of figures would, of course, have increased the price of the book, but might have helped the visually orientated reader. Not the least valuable part of the book is the bibliography of the references, though many will regret that this is not arranged alphabetically. These are small criticisms of an excellent book which will find an essential place on the bookshelf of any clinician interested in chest diseases.

C. M. Fletcher.

METAL AND BONE

Metals and Engineering in Bone and Joint Surgery. By Charles Orville Bechtol, M.D., Albert Barnett Ferguson, jun., M.D., and Patrick Gowans Laing, M.B., B.S., F.R.C.S. (Pp. 186+vii; illustrated. 64s.) London: Baillière, Tindall and Cox, Ltd. 1959.

This book is the outcome of work done at the Universities of California and Pittsburgh by three orthopaedic surgeons, whose interest in the biochemical

field did not overlap. The biological and engineering principles involved in the study of repair of fractures with and without the use of internal fixation has attracted attention recently, and the type of experimental work described is important.

The surgeon who reads this book can make himself as familiar with the uses and misuses of metal for internal fixation as he is with skeletal anatomy. He will find that scientific thought has been given to the structure of bone and how this is affected by injury and by the application of various types of metal. Information on the advantages of particular metal, plates, screws, bands, and wire is given with instructions on the use and care of metal required for internal fixation. It is pointed out that considerable responsibility rests on the surgeon when he has to decide not only whether an operation is advisable, but also whether one necessitating the insertion of internal fixation is desirable, and what type of metal should be chosen. There is evidence that metal is badly chosen and also that it may be wrongly placed on a bone. Research has shown that it may not be recognized that a fracture is still mobile after internal fixation, or that ambulation has been started too early. In fact, the metal inserted may be blamed for delayed or non-union, when other factors were entirely or largely the cause.

The description of replacement of living tissue is one of the fascinating studies made possible by present-day methods of research. The surgeons, one of whom was trained in this country, are to be congratulated for reporting their scientific study of bone and metal in such a manner that can be easily understood, particularly with the help of well-chosen illustrations and an engineering–orthopaedic glossary. This book can be studied advantageously by all doing both acute and chronic repair work on bones and joints.

ST. J. D. BUXTON.

RENAL METABOLISM

Metabolic Aspects of Renal Function. By William D. Lotspeich, M.D. (Pp. 214+xiv; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Quantitative studies by clearance techniques have provided a satisfactory description of the principal excretory and homoeostatic functions of the kidney, although they have often failed to apportion precisely the contribution of glomeruli and of tubules to a particular process. During the last 15 years increasing efforts have been made to study the tubules by defining the biochemical events that underlie specific tubular functions. The particular functions so far studied by this new approach have been determined partly by chance, largely by the availability of simple techniques such as use of the renal cortical slice, and also by the parallel advances made in the study of cellular transport in a variety of biological systems. Dr. Lotspeich, who has worked in several branches of renal biochemistry, has gathered together in this monograph much information that is otherwise scattered in physiological and biochemical journals. His review is selective, but he has drawn extensively on relevant general biological studies and he has not hesitated to indulge in provocative speculation. Individual chapters provide reasonably concise and accurate accounts of the action of phlorizin, the formation and secretion of ammonia, and the tubular transport of organic acids and bases, of phosphate, amino-acids, and glucose. The treatment of the tricarboxylic cycle is less satisfactory and even confusing. The unenlightened reader will remain uncertain whether potassium deficiency is associated with increased or with decreased excretion of citric and α-oxoglutaric acids; he is also told that potassium depletion "reduces the capacity to reabsorb bicarbonate in the kidney," whereas the converse is true.

A pleasantly readable text is marred by careless proofreading. The legends of Figs. 3 and 4 are inverted; the sulphur atom in the abbreviated formula for the acyl mercaptans of co-enzyme A appears twice as –S–; divalent carbon appears to result from the oxidative deamination of amino-acids. These criticisms do not detract seriously from a commendable attempt to impose a little order on a diffuse and rapidly expanding branch of the study of the kidney.

S. W. STANBURY.

ELECTROTHERAPY FOR STUDENTS

Practical Electrotherapy for Physiotherapists. By Brenda Savage, M.Sc., M.C.S.P. (Teacher's Certificates). (Pp. 296; illustrated. 30s.) London: Faber and Faber, Ltd. 1960.

In this book one can trace the discrepancies between traditional physiotherapeutic lore and the tenets of scientific medicine. The fact that its author holds the degree of M.Sc. as well as the teacher's diplomas of the Chartered Society of Physiotherapy adds to its interest. In her preface she tells us that her conclusions as to the efficacy of the treatments she describes have been arrived at purely by clinical assessment, as the physiotherapist does not have the time or money to make a statistically significant survey. This excuse no longer impresses the medical profession.

The first half of the book is devoted to chapters on the physiological effects of electrical currents and on the techniques of their application in treatment. These are described with great attention to detail and at the same time are readable and easily understood. The medical profession, however, will not accept the suggested indications for these methods of treatment without some reservation, and it is obvious that the author is aware of this even if she still mentions that magnesium ionization is used in the treatment of recent injuries and that iodide ions have a fibrolytic effect.

The second half of the book is devoted to various conditions and their treatment by electricity, which here includes the infra-red and ultra-violet radiations. Practitioners of all branches of medicine will be surprised by some of the treatments advocated in a book such as this. For instance, the treatment of tinea pedis is by copper or silver ionization, Bell's palsy can be treated by ultra-violet counter irritation, and the treatment of rickets is general ultra-violet irradiation combined with a diet rich in vitamin D. In some of her claims the author is almost naive. There is an index, but, unfortunately, although the names of doctors are scattered through the book, no dates or references are given.

This book will help the student of physiotherapy who is not taught to be critical, but the specialist in physical medicine or the general physician will stumble over many of the statements that are made.

W. TEGNER.

A BISHOP'S SENSE AND NONSENSE

The Surgery of Theodoric, ca. 1267. Translated from the Latin by Eldridge Campbell, M.D., and James Colton, M.A. Volume 2 (Books III and IV). (Pp. 233+xix. $5.50.) New York: Appleton-Century-Crofts, Inc. 1960.

Five years ago Eldridge Campbell and James Colton translated the first two books of the *Surgery of Theodoric*, Bishop of Cervia, who flourished about A.D. 1267. That volume contained the remarkable description of aseptic wound-treatment, a vision of the truth which was too far ahead of the time to become generally adopted. The same authors have now translated the rest of Theodoric's work, though, unfortunately, Dr. Campbell did not live to see the publication of this second volume, which deals with fistulae, abscesses, cancer, tumours, herniae, and other general surgical conditions.

The surgery of 700 years ago was a curious mixture of practical common sense and theoretical nonsense. The Bishop was wiser than his writings, for, after a long description in which drugs and mumbo-jumbo were mingled, he adds, "perchance their faith help them." For the modern doctor the old humoral pathology complicates matters. One can understand that "a boil is a kind of hot abscess" and can marvel that "erysipelas is an imposthume from fiery bile," but how difficult it is to follow that "the material causes of an imposthume are six: the four humors and superfluities of fluid and wind."

Theodoric gives excellent descriptions of fistula in general, and fistula-in-ano in particular, and special accounts are given of operations for stone in the bladder and for umbilical and inguinal hernia. He preferred the cautery to the knife in operations for hernia, and recommends, in view of the fact that "death can follow very easily," that the doctor should not undertake this cure with any desire of financial return "except when he has been asked by the patient, and then in his presence and the presence of his friends (or at least in the presence of his friends) he has made clear the eminent danger."

There is much to enjoy, much to puzzle over, and a good deal to be thankful for, in the reading of this book.

ZACHARY COPE.

Pneumoconiosis Abstracts, Volume III, contains abstracts reproduced from the *Bulletin of Hygiene* for the years 1951 to 1955. It continues the sequence established by the previous volumes—covering the period from 1926 to 1950—and the set therefore provides in tablet form the important papers published in the field of pneumoconiosis over a period of 30 years. Also included are abstracts of articles on dust. (Pitman Medical Publishing Co., Ltd.; 376+viii pp.; index of authors or sources, and of subjects; 65s.)

The *Handbook of Diet Therapy*, written and compiled by Dorothea Turner for the American Dietetic Association, is now in its third edition. It includes new chapters on diet during pregnancy, adolescence, and old age; energy expenditure; fatty acid modifications; and phenylalanine restrictions; while the chapters on the sodium-restricted diet, the low- and high-calorie diets, and the soft and low-fibre diets have been completely revised. There is a comprehensive chapter on "Interviewing the Patient" by Margaret Read, which recognizes that the dietitian must be able to translate her knowledge of the basic principles of nutrition into the practical terms of each patient's everyday life. (Cambridge University Press, 1959; 222+xv pp.; index; price £1 17s. 6d.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Klinik und Therapie der Nebenwirkungen. Sulfonamide-Antibiotica - Tuberculostatica - Cytostatica - Anticoagulantien-Hormone - Vitamine. Edited by H. P. Kuemmerle, A. Senn, P. Rentchnick, and N. Goossens, with 27 contributors. (Pp. 1,286+xx; illustrated. DM. 148.) Stuttgart: Georg Thieme Verlag. 1960.

The Detection of Secret Homicide. A Study of the Medico-legal System of Investigations of Sudden and Unexplained Deaths. By J. D. J. Havard, M.A., LL.B., M.B., B.Chir. (Pp. 253+xv. 35s.) London: Macmillan and Co., Ltd. New York: St. Martin's Press. 1960.

Surgical Anatomy of the Bronchovascular Segments. By William E. Bloomer, M.D., Averill A. Liebow, M.D., and Milton R. Hales, M.D. (Pp. 273+xi; illustrated. £6 12s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Recent Progress in Hormone Research. Proceedings of the Laurentian Hormone Conference 1959. Edited by Gregory Pincus. Volume XVI. (Pp. 608+viii; illustrated. $14.) New York and London: Academic Press. 1960.

Hemophilia and other Hemorrhagic States. International Symposium, Rome. Edited by Kenneth M. Brinkhous, M.D. Assistant editor: Pietro de Nicola, M.D. (Pp. 266+xx; illustrated. 60s.) Chapel Hill, North Carolina University Press. London: Oxford University Press. 1960.

Advances in Oto-Rhino-Laryngology. Edited by Professor Dr. L. Rüedi. Volume VI. With 8 contributors. (Pp. 248+viii; illustrated. Sw. fr. 60.) Basle, New York: S. Karger. 1960.

Search for Security. An Ethno-psychiatric Study of Rural Ghana. By M. J. Field. (Pp. 478. 42s.) London: Faber and Faber. 1960.

The Heart in Industry. By 24 authors. Edited by Leon J. Warshaw, M.D., F.A.C.P. (Pp. 677+xix. $16.) New York: Paul B. Hoeber, Inc. 1960.

Blood Flow in Arteries. By Donald A. McDonald, M.A., D.M.(Oxon.), D.Sc.(London.). (Pp. 328+xi; illustrated. 40s.) London: Edward Arnold (Publishers) Ltd. 1960.

Das Menschliche Knochenmark. Anatomie, Physiologie und Pathologie nach Ergebnissen der Intravitalen Markpunktion. By Professor Dr. Karl Rohr. Third edition. (Pp. 593+xvi; illustrated. DM. 98.) Stuttgart: Georg Thieme Verlag. 1960.

Proceedings of the Isra Symposium on the Social Aspects of Chronic Rheumatic Joint Affections. Especially Rheumatoid Arthritis. Amsterdam, October 13-14, 1959. Edited by G. van Dam and W. Hijmans. (Pp. 132; illustrated.) Amsterdam, New York: Excerpta Medica Foundation. 1960.

Intra-osseous Venography. By Robert A. Schobinger, M.D. (Pp. 243+x; illustrated. $14.50.) New York and London: Grune and Stratton. 1960.

The Problem of Acute Hypothermia. Edited by P. M. Starkov. Translated from the Russian by R. E. Hammond. Editor: Professor E. Neil. (Pp. 319; illustrated. 70s.) London, Oxford, New York, Paris: Pergamon Press. 1960.

Modern Trends in Occupational Health. Edited by R. S. F. Schilling, M.D., M.R.C.P., D.P.H., D.I.H. (Pp. 313+ix; illustrated. 67s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Neurology. By Roy Grinker, M.D., Paul C. Bucy, M.D., and Adolph L. Sahs, M.D. Fifth edition. (Pp. 1,386+xi; illustrated. £9 16s.) Oxford: Blackwell Scientific Publications. 1960.

Roentgen Examinations in Acute Abdominal Diseases. By J. Frimann-Dahl, M.D., Ph.D. (Pp. 518+xiv; illustrated. £6 4s.) Oxford: Blackwell Scientific Publications. 1960.

Stress and Cellular Function. By H. Laborit, M.D., in collaboration with M. Cara, M.D., D. Jouasset, M.D., C. Duchesne, M.D., and G. Laborit, M.D. (Pp. 255+xi; illustrated. 60s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co., Ltd. 1960.

Cosmetic Surgery. Principles and Practice. By Samuel Fomon, M.D. (Pp. 651+xvii; illustrated. £11.) Philadelphia, Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co., Ltd. 1960.

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RHEUMATIC HEART DISEASE IN CHILDREN

A further joint report from Great Britain and the U.S.A. on rheumatic heart disease in children appears in the opening pages of the *Journal* this week. It is a sequel to the report[1] published in 1955, and it records the subsequent history of the same groups of patients during a follow-up period of five years. The teams of British and American investigators responsible for this important inquiry have been highly successful in keeping track of their patients, for they are able to give information about 461 (92.7%) of their original 497. Of these 461 cases, 16 were known to have died; and the status of the heart was recorded in all but 19 of the living patients. These are impressive figures, and constitute a suitable basis for an inquiry which has been carefully planned and conducted, both clinically and statistically.

Briefly, the object of the study was to compare the relative merits of A.C.T.H., cortisone, and aspirin (each given according to a specified plan for six weeks) in the treatment of rheumatic infection and in the prevention of rheumatic heart disease. The present report deals mainly with the second of these questions, and the conclusion is reached that prognosis was not influenced more by one treatment than another. Clinicians have for many years thought that the course of rheumatic carditis is uninfluenced by salicylates; and now we learn that hormone treatment, when given in the dosage used in this trial, is equally ineffective. Perhaps larger dosage, adjusted to the age and weight of the patient,[2] and possibly combined with high dosage of salicylates, might prove to be helpful. But both treatments have their dangers, and further clinical trials would need to be planned and carried out with caution. The report stresses that the treatment of acute rheumatic infection cannot be properly evaluated unless the status of the heart at the start of treatment is taken closely into account.

Perhaps the chief value of this excellent report will be to focus attention yet again on the cardinal importance of *preventing*, whenever possible, the primary rheumatic infection—a subject that has received much attention in recent years.[3] Nowadays the risk of permanent heart disease developing from an initial infection seems small; but one infection invites recurrences, and with each return of the illness the danger to the heart increases. Our main problem at the present time—and it is linked closely with the question of prophylaxis—is to recognize with certainty the beginning of a rheumatic infection; and the difficulties of early diagnosis have increased as childhood rheumatism has become less frequent and less characteristic when assessed by earlier clinical standards. If the disease is to be prevented and cardiac damage avoided, the possibility of its occurrence must be considered while the patient is still in the home environment. A child has a sore throat, or a head cold (with or without otitis media), or some slight pyrexia with fleeting discomfort in joints—perhaps an indefinite malaise, with apathy and loss of colour. Is this patient developing rheumatic infection? The family doctor carries a heavy responsibility and there is no single test to give him the answer. Throat-swab examination for haemolytic streptococci, and other laboratory tests such as the erythrocyte sedimentation rate, C-reactive protein, serum protein fractions, and antistreptolysin reaction (if arrangements for these can be made), may serve as pointers but do not give a clear "yes" or "no." The difficulties of coming to a firm diagnosis even when the patient is in a well-equipped hospital were exemplified by K. A. Hallidie-Smith and E. G. L. Bywaters,[4] who reported on 2,214 patients admitted to the Rheumatism Research Unit at Taplow during a nine-year period. Only 959 were discharged with the diagnosis of rheumatic fever, and many of these evidently required a period of careful observation and examination before the diagnosis could be established with certainty.

Some practitioners give penicillin, or another antibiotic according to clinical circumstances, to every child whom they suspect of harbouring a streptococcal infection, using the argument that at the present time nobody could do more to ward off acute rheumatism. This may be sound policy, especially in districts—for example, large industrial areas—where rheumatic infection has always been a menace, even if it is receding now. But the widespread use of antibiotics is well known to have its own disadvantages and dangers; and J. Fry's[5] interesting paper reporting the treatment of acute tonsillitis and acute otitis media shows that in his

[1] *Brit. med. J.*, 1955, 1, 555.
[2] Illingworth, R. S., in *Recent Advances in Paediatrics*, ed. D. Gairdner, 1958, p. 311. London.
[3] See *Brit. med. J.*, 1959, 1, 351.
[4] Hallidie-Smith, K. A., and Bywaters, E. G. L., *Arch. Dis. Childh.*, 1958, 33, 350.
[5] Fry, J., *Brit. med. J.*, 1958, 2, 883.
[6] *Circulation*, 1955, 11, 317

practice (Beckenham, Kent) there were no real complications (and no rheumatic fever) either in the cases treated with antibiotics or in those treated with non-specific measures. He treated 106 cases of non-streptococcal tonsillitis under the age of 20 years, giving antibiotics to 12 only; and 133 cases of haemolytic streptococcal tonsillitis, of whom only 24 received antibiotics. Admittedly if these latter patients had happened to live in another district there might have been rheumatic complications. According to the American Heart Association's figures[6] one might have expected about 3 to turn up among the 109 haemolytic streptococcal cases not treated with antibiotics.

The use of antibiotics certainly does not give complete protection against rheumatic infection, and we need to know more about causative factors other than haemolytic streptococci. It would seem reasonable to urge that, in districts where rheumatic infection arises most frequently, practitioners should be encouraged to make full use of the domiciliary diagnostic services available to them. In those areas where the necessary pathological services are not easily obtained in the home, there should be further consultation between the appropriate authorities.

STEATORRHOEA

The small intestine, for so long an almost unknown territory for the investigator, is the subject of steadily increasing medical interest. New techniques such as biopsy, new apparatus such as the so-called "radio pill" (radiosonde), and the study of the absorption of xylose, folic acid, vitamin B_{12}, and isotopically labelled substances have led to the acquisition of much new physiological and pathological knowledge. In his Goulstonian lectures, published recently in this journal, Dr. J. Badenoch[1] has given a very complete review of the clinical features of steatorrhoea in the adult, and this both shows the progress made in understanding this group of diseases and also poses a number of still unanswered questions. In his own material of 163 cases there were eleven different diseases responsible, though the great majority of his patients were cases of idiopathic steatorrhoea. In many of them diarrhoea was not a presenting symptom, and the possible variations in the clinical picture are endless. One fairly common complication was subacute obstruction: this was seen in ten patients who had no obvious permanent narrowing of the bowel and three of whom died of volvulus. It is worth remembering that various deficiency states, such as osteomalacia and hypoprothrombinaemia, can occur in any case of steatorrhoea and are not confined to the iodiopathic group. Badenoch suggests that poor absorption may not be the only cause of iron deficiency in these patients but that seepage of serum or increased mucosal desquamation may be contributory factors, particularly in the child with coeliac disease. Despite increased knowledge the neuropathy from which some of these patients suffer can still not be cured and some deaths from malnutrition cannot be prevented.

In idiopathic steatorrhoea it is impossible to tell which patients will respond to a gluten-free diet, and the mechanism by which gluten acts is still not understood. It seems that patients with this disease lack the ability to prevent some product of gluten passing through the mucosa in a toxic form, for R. Schneider and his colleagues[2] have shown that the toxic fraction of gluten will inhibit peristalsis of an isolated strip of bowel if it is applied to the serosa but not if instilled into the lumen, and that incubation with normal jejunal mucosa will prevent this toxic action. It is possible that patients who are not gluten-sensitive suffer from the effects of some other similar failure of detoxication by the mucosal cell.

The part played by bacteria in steatorrhoea is still not completely elucidated. It is now known that in the blind-loop syndrome and jejunal diverticulosis the administration of antibiotics can nearly always improve the ability to absorb vitamin B_{12}, but the effect on the steatorrhoea is much less predictable. Similarly, while stagnation and bacterial overgrowth in the small bowel are thought to occur in steatorrhoea associated with partial gastrectomy, the precise importance of this is unknown, and it may be the consequence rather than the cause of the steatorrhoea. When the part played by bacteria is being considered it is as well to remember that neomycin may sometimes cause steatorrhoea as well as cure it.

Because of the diagnostic significance of abnormal fat excretion it is clearly important to know the limits of normality, and yet there is still doubt about the best criteria to adopt. In last week's *Journal* Dr. E. B. Hendry[3] re-examined the relative merits of estimating the percentage of fat in the faeces and the total output of fat in 24 hours. Using a Soxhlet apparatus for extraction, he examined 231 specimens from 138 patients suspected of having steatorrhoea: he excluded cases in which the diagnosis was clearly

[1] Badenoch, J., *Brit. med. J.*, 1960, **2**, 879 and 963.
[2] Schneider, R., Bishop, H., and Shaw, B., *Brit. J. Pharmacol.*, 1960, **15**, 219.
[3] Pimparkar, B. D., Tulsky, E. G., Kalser, M. H., and Bockus, H. L., *Brit. med. J.*, 1960, **2**, 894.
[4] Hendry, E. B., ibid., 1960, **2**, 975.
[5] Crane, C. W., and Neuberger, A., ibid., 1960, **2**, 815 and 888.
[6] Sperry, W. M., *J. biol. Chem.*, 1929, **81**, 299.

established on clinical grounds. The arbitrary limits of normality were taken as 25% for the proportion of fat and a daily excretion of 5 grammes. By both these criteria 159 of the tests were considered normal and 23 to indicate indisputable evidence of steatorrhoea, but in the remaining 49 fat balances the results of one test fell within the normal limits while the other was abnormal. Hendry shows that these discrepancies were very largely due to variations in the total dried weight of the faeces, which was exceptionally low when the proportion of fat exceeded 25%, though the total 24-hour output was normal. It seems, therefore, that the 24-hour output of total fat is the more reliable indicator of steatorrhoea.

Another useful critical appraisal of the diagnostic criteria in steatorrhoea comes from Dr. B. D. Pimparkar and his fellow workers,[4] who have compared the results of estimating the faecal and plasma radioactivity after administration of ^{131}I-labelled triolein with the chemical estimation of faecal fat. The use of isotope tests of one kind or another in the diagnosis of steatorrhoea has increased greatly, and consequently an assessment of their reliability is important. Pimparkar and his colleagues show that the administration of the triolein as an emulsion is to be preferred to the use of a capsule and that the estimation of residual faecal radioactivity is more reliable than the measurement of the peak blood activity. The latter is influenced by the rate of absorption as well as by the total amount absorbed. The main interest of this paper, however, lies in the fact that both the isotope tests failed to establish a diagnosis of steatorrhoea in a significant number of cases, even though the chemical criterion of abnormality was taken to be an excretion of over 7 grammes in 24 hours, a figure higher than that taken by others. Thus, although these tests, because of their administrative convenience, are useful for diagnosis, chemical estimation will remain necessary in many borderline cases as well as for the accurate measurement of the degree of steatorrhoea and for assessing the results of treatment.

In the past very little attention has been paid to the absorption of nitrogen in patients with steatorrhoea. Now in two papers recently published in this journal Drs. C. W. Crane and Professor A. Neuberger[5] have reported an extensive investigation into protein digestion and nitrogen absorption in normal subjects and in four patients with idiopathic steatorrhoea. They used yeast protein, both whole and after hydrolysis, which had been labelled with the stable isotope ^{15}N. This was estimated in faeces, urine, and plasma in a mass spectrometer. This method clearly has great possibilities. In the patients with steatorrhoea the rate of absorption, as was to be expected, was considerably slower than in the normal subjects. The difference was more marked for whole protein than for the hydrolysate, and it seems possible that in idiopathic steatorrhoea there may be both a reduction in the absorptive area which is rarely reversible and a deficiency of peptidases in the mucosal cell which can be overcome in some way when a gluten-free diet is given. Further experiments reported by Crane and Neuberger throw much new light on the source of faecal nitrogen. It appears that a large amount of this may be endogenous, being derived from the various secretions of the intestinal tract rather than from food. There is evidence from various sources, such as the work of W. M. Sperry[6] with dogs on a fat-free diet, that endogenous fat is excreted in significant amounts by the bowel, though the site of origin is still obscure. Now it seems that much of the nitrogen may also be endogenous.

PACKAGE DEAL COMPLETED

On September 28 a Special Representative Meeting tied the final knot on the package deal. With one dissentient and a few abstainers, it voted in favour of the Council's recommendation that the reports of the Joint Working Parties and the Minister's offer to implement the recommendations of the Royal Commission as a whole and as they stand be accepted. On the previous day a Special Conference of Local Medical Committees, speaking for general practitioners, endorsed a similar recommendation from the General Medical Services Committee, and on September 13 the Joint Consultants Committee, with the blessings of its constituent bodies in its pocket, unanimously voted for acceptance on behalf of hospital medical staff, though the announcement of this decision was deferred until September 28. By hard work in what is normally the medico-political off-season, the Working Parties have done their job with commendable speed, and for this the profession's representatives, led by Mr. T. Holmes Sellors and Dr. A. B. Davies, deserve the gratitude of their colleagues. General practitioners should begin to get their retrospective payments in the middle of next month, but certain complications will delay the back payments to hospital medical staff until early in the New Year. In both cases payments on the new scales should begin early in 1961, backdated, as the Royal Commission recommended, to January 1, 1960.

[1] *Brit. med. J., Supplement*, 1960, 2, 115.

Unanimous approval of the Working Parties' proposals for distributing the Royal Commission's recommended 22.5% average increase in remuneration could not be expected. This was particularly so in general practice, where the system of payments is so complicated. As the reports in this week's *Supplement* of the debates at the S.R.M. and Special Conference show, rural practitioners were unhappy about the standstill agreement on the amount of the fund from which they draw additional payments. Small-list practitioners wanted a better deal from the special loadings on capitation fees, for they, like the big-list practitioners, get proportionately less of the increase. Some thought the increase in the obstetric fee too large, others wanted more. On the hospital side the increase in board-and-lodging charges for residents came in for criticism, as did the survival of the peculiar, pin-pricking rule that whole-time consultants should receive no fee for the first eight domiciliary consultations in any one quarter. The domiciliary consultation fee, too, remains the same as it was in 1948. The abolition of weighting payments to part-time consultants caused concern to those who see in it a threat to the principle that independent private practice should be encouraged. This is one of the matters which the Joint Consultants Committee intends to bring before the Review Body as soon as possible.

The difficulties under which the medical members of the Joint Working Parties had to work were apparent. They had had to negotiate agreement with the Ministry's representatives on the distribution of limited sums of money in accordance with the recommendations and "hopes" of the Royal Commission. Some of these were incompatible and some were open to differing interpretations. When the two sides of the Working Parties differed the consequences of failure to agree were all too real to the medical side, for it would have meant the end of the package deal, and the profession had already waited four years for its money. For these reasons those who thought they had come off badly in the share-out were ready to modify their protests. But criticism of the Ministry for insisting on introducing into the package deal some completely new proposals for distributing general-practitioner remuneration to provide incentives to good practice was not inhibited by any such feelings. What these proposals were is far from clear, but Dr. Davies and his colleagues in the Working Party resisted them. Eventually, to save a breakdown in negotiations, they agreed to £1m. of the award being held back from distribution "so that further consideration can be given to methods of making the best possible general medical service available to the public." A further Working Party is to pursue this matter. There were more motions on the agendas against this proposal than against any other. Representatives accepted it partly because failure to do so would have negatived all the other recommendations, including those for hospital staff, and partly because of a last-minute letter from the Ministry explaining that it was not intended that this money should accumulate from year to year until a scheme for its use had been agreed. It would be distributed at the end of each year until agreement had been reached. When the S.R.M. had agreed to accept the Working Parties' reports and the Minister's offer, debate ceased to be fettered by fears that this or that amendment might be a wrecking one, and it returned to the attack on the reserved £1m. It carried by 161 votes to 137 a motion by Dr. C. M. Scott (Barnet) deploring the proposal.

The profession will be glad to be at the end of its stormy passage through the last four years. What the future will bring will largely depend on the Review Body. Dr. Rowland Hill has recently pointed out[1] that the Review Body was generally thought to be the most important feature of the Royal Commission's report, yet it had been the subject of least consideration. With its appointment imminent, the profession will be giving much thought to its relations with the body to whom it must now look to guard its interests.

DENTAL IMPLANTS

The treatment of patients who have persistent difficulty in wearing dentures would be simplified if a metal implant could be attached to the bone of the jaw with metal abutment posts, penetrating through the mucous membrane into the mouth, to which artificial dentures could be attached. Sporadic attempts have been made down the years to implant various metals, mostly into the sockets of extracted teeth, without success.

In 1936 C. S. Venable and colleagues[1] showed that an alloy of cobalt, chromium, and molybdenum termed "vitallium" was physiologically compatible with the body tissues and their fluids, and orthopaedic surgeons began to use it for a variety of purposes, implanting it into the tissues and fixing it to the bone by screws. In 1943 G. S. A. Dahl[2] inserted a metallic bar subperiosteally on to the surface of the alveolar bone of the maxilla with four posts projecting through the mucosa. In 1948 N. I. Goldberg and A. Gershkoff[3] inserted their first dental implant, which consisted of a cast vitallium base with four projecting posts. The mucosa of the mandibular alveolar process was reflected and the base of the implant laid directly on to the bone and held in place with screws. This implant was placed by a one-stage operation—that is, the implant was shaped to a

[1] Venable, C. S., Stuck, W. G., and Beach, A., *Ann. Surg.*, 1937, **105**, 917.
[2] Dahl, G. S. A., *Odont. T.*, 1943, **51**, 440.
[3] Goldberg, N. I., and Gershkoff, A., *Dent. Dig.*, 1949, **55**, 490.
[4] Mack, A., *Brit. dent. J.*, 1955, **99**, 287.
[5] —— ibid., 1960, **108**, 217.
[6] Trainin, B., ibid., 1957, **102**, 389.

model of an impression of the surface of the mandible taken over the mucous membrane, the model having been previously trimmed to what was considered to be the shape of the underlying bone.

The weakness of this technique was that the implants fitted the bone surface very inaccurately and the solid nature of the base interfered with the healing of the mucosa. The two-stage operation and the open mesh-work base were therefore developed to overcome these difficulties. At the first operation the muco-periosteum is widely reflected and an impression taken of the surface of the exposed bone. On the model cast from this impression the implant framework is constructed, care being taken to ensure that the framework is as open as possible compatible with strength and that the minimum of metal lies in the area of the suture line. About three weeks later the mucosa is again reflected and the implant inserted. The mucosa is reunited with sutures and the periosteal fibres reattach themselves to the surface of the bone through the mesh of the framework of the base, binding the implant firmly to the bone, the four abutment posts protruding through the mucosa, which heals firmly round them. By this technique several hundred successful implants have been inserted throughout the world during the last 10 years, many of them having been in place for five years or more.

In Great Britain the development of dental implants is associated with the names of A. Mack,[4,5] B. Trainin,[6] and Talmadge Read among others. Mack has shown in experiments on monkeys that the subperiosteal framework of the implant probably becomes surrounded by epithelium.

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Both these reports call for further research, for there is still much to be learnt about the extent and nature of the hazard. Many medical men also consider that the time is ripe for more effective preventive action than has so far been taken, and would agree with these words from the Tuberculosis Council's report: "The Council would urge upon those in authority that we are faced with a health problem of great magnitude and that not enough has been done centrally to safeguard the public welfare. Is it really in the public interest to allow unrestricted advertisement of a substance which reliable evidence suggests is dangerous to health? Are the preventive steps already taken commensurate with the gravity of the situation? In the opinion of the Council they fail to meet this requirement. More thought, money, and effort are necessary in the attempt to prevent the serious diseases associated with smoking." Moreover, the lead that doctors themselves can give must surely be helpful. A questionary sent to 50 chest hospitals and 50 chest clinics elicited 85 replies. Of these, 60 stated that medical staff did not smoke while on duty and in view of patients. This would seem to be an example worth encouraging.

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Unanimous approval of the Working Parties' proposals for distributing the Royal Commission's recommended 22.5% average increase in remuneration could not be expected. This was particularly so in general practice, where the system of payments is so complicated. As the reports in this week's *Supplement* of the debates at the S.R.M. and Special Conference show, rural practitioners were unhappy about the standstill agreement on the amount of the fund from which they draw additional payments. Small-list practitioners wanted a better deal from the special loadings on capitation fees, for they, like the big-list practitioners, get proportionately less of the increase. Some thought the increase in the obstetric fee too large, others wanted more. On the hospital side the increase in board-and-lodging charges for residents came in for criticism, as did the survival of the peculiar, pin-pricking rule that whole-time consultants should receive no fee for the first eight domiciliary consultations in any one quarter. The domiciliary consultation fee, too, remains the same as it was in 1948. The abolition of weighting payments to part-time consultants caused concern to those who see in it a threat to the principle that independent private practice should be encouraged. This is one of the matters which the Joint Consultants Committee intends to bring before the Review Body as soon as possible.

The difficulties under which the medical members of the Joint Working Parties had to work were apparent. They had had to negotiate agreement with the Ministry's representatives on the distribution of limited sums of money in accordance with the recommendations and "hopes" of the Royal Commission. Some of these were incompatible and some were open to differing interpretations. When the two sides of the Working Parties differed the consequences of failure to agree were all too real to the medical side, for it would have meant the end of the package deal, and the profession had already waited four years for its money. For these reasons those who thought they had come off badly in the share-out were ready to modify their protests. But criticism of the Ministry for insisting on introducing into the package deal some completely new proposals for distributing general-practitioner remuneration to provide incentives to good practice was not inhibited by any such feelings. What these proposals were is far from clear, but Dr. Davies and his colleagues in the Working Party resisted them. Eventually, to save a breakdown in negotiations, they agreed to £1m. of the award being held back from distribution "so that further consideration can be given to methods of making the best possible general medical service available to the public." A further Working Party is to pursue this matter. There were more motions on the agendas against this proposal than against any other. Representatives accepted it partly because failure to do so would have negatived all the other recommendations, including those for hospital staff, and partly because of a last-minute letter from the Ministry explaining that it was not intended that this money should accumulate from year to year until a scheme for its use had been agreed. It would be distributed at the end of each year until agreement had been reached. When the S.R.M. had agreed to accept the Working Parties' reports and the Minister's offer, debate ceased to be fettered by fears that this or that amendment might be a wrecking one, and it returned to the attack on the reserved £1m. It carried by 161 votes to 137 a motion by Dr. C. M. Scott (Barnet) deploring the proposal.

The profession will be glad to be at the end of its stormy passage through the last four years. What the future will bring will largely depend on the Review Body. Dr. Rowland Hill has recently pointed out[1] that the Review Body was generally thought to be the most important feature of the Royal Commission's report, yet it had been the subject of least consideration. With its appointment imminent, the profession will be giving much thought to its relations with the body to whom it must now look to guard its interests.

DENTAL IMPLANTS

The treatment of patients who have persistent difficulty in wearing dentures would be simplified if a metal implant could be attached to the bone of the jaw with metal abutment posts, penetrating through the mucous membrane into the mouth, to which artificial dentures could be attached. Sporadic attempts have been made down the years to implant various metals, mostly into the sockets of extracted teeth, without success.

In 1936 C. S. Venable and colleagues[1] showed that an alloy of cobalt, chromium, and molybdenum termed "vitallium" was physiologically compatible with the body tissues and their fluids, and orthopaedic surgeons began to use it for a variety of purposes, implanting it into the tissues and fixing it to the bone by screws. In 1943 G. S. A. Dahl[2] inserted a metallic bar subperiosteally on to the surface of the alveolar bone of the maxilla with four posts projecting through the mucosa. In 1948 N. I. Goldberg and A. Gershkoff[3] inserted their first dental implant, which consisted of a cast vitallium base with four projecting posts. The mucosa of the mandibular alveolar process was reflected and the base of the implant laid directly on to the bone and held in place with screws. This implant was placed by a one-stage operation—that is, the implant was shaped to a

[1] Venable, C. S., Stuck, W. G., and Beach, A., *Ann. Surg.*, 1937, **105**, 917.
[2] Dahl, G. S. A., *Odont. T.*, 1943, **51**, 440.
[3] Goldberg, N. I., and Gershkoff, A., *Dent. Dig.*, 1949, **55**, 490.
[4] Mack, A., *Brit. dent. J.*, 1955, **99**, 287.
[5] —— ibid., 1960, **108**, 217.
[6] Trainin, B., ibid., 1957, **102**, 389.

model of an impression of the surface of the mandible taken over the mucous membrane, the model having been previously trimmed to what was considered to be the shape of the underlying bone.

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"Fracture around the Wrist," by Professor J. H. Kellgren on "The Diagnosis and Treatment of Osteoarthritis," and by Dr. Maurice Partridge on "The Anti-depressant Drugs." Further details are given on p. 1101 in this issue. There will be a period for questions and discussion at each of these meetings, and the Association's Science Committee is to be congratulated for promoting this useful new attraction for members.

NEW CHAIR OF CHILD HEALTH

The creation of a new chair of child health in the University of London is timely. The National Spastics Society has endowed it on a munificent scale with £2m., and the Royal President of the Society has consented to the chair being named after him as the Prince Philip Chair of Paediatric Research. It will be established at Guy's Hospital, with Dr. Paul E. Polani as professor. Now that infectious diseases constitute so much less of a hazard in childhood than formerly, the harm done by those which are congenital or traumatic in origin is the more evident. Despite the great success that has crowned the new methods of surgical treatment in, for example, the congenital malformations of the heart, many crippling disorders of childhood, especially perhaps of the nervous system, still present a baffling problem to research. Some of the work going on in this field is the subject of a report in the *Journal* at p. 1082. Dr. Polani's interest in the aetiology and treatment of cerebral palsy will find full scope in his new appointment. He takes it up after working on these and other problems of childhood disease at Guy's Hospital since 1948, when he came to Britain as a postgraduate student after qualifying at the University of Pisa.

SAFETY IN GAS COOKERS

The annual number of deaths from coal-gas poisoning has been increasing for many years. The increase seems to be greater than would be expected from having a higher proportion of old people in the population and a more extensive supply of gas.[1] A B.M.A. committee set up to inquire into the detailed causes of this mortality recommended among other things that automatic safety devices should be developed and popularized.[2] The Gas Council has been at work on this and has introduced two forms of gas cooker, designated GC.1 and GC.2, specially designed to assist physically handicapped people, including the elderly and infirm. Both cookers incorporate two boiling burners and a grill, which will light automatically when the appropriate gas tap is turned on. Special devices prevent the main gas leaving any burner, including that for the oven, unless a pilot flame is alight to provide ignition. The taps have long levers which can be operated without grasping the handle with the fingers, but can be turned with the elbow or back of the hand. The oven thermostat also has a lever extension and the numbered settings can be identified by touch and hearing. The GC.1 is a vertical model, with hotplate, grill, and oven in descending order, while the GC.2 is of horizontal design and can be installed at any height convenient to a person confined to a wheel-chair or prevented in some other way from bending down to cook.

As well as selling these cookers in the ordinary way the Gas Council will hire them at a low rental if a patient's age or physical or mental disability makes their use advisable. When a person is receiving national assistance, the local National Assistance Board will be able to recommend that a special cooker should be supplied on hire; for people not on national assistance an application for hire should be supported by a recommendation from the medical officer of health, to whom the family doctor may wish to refer suitable cases. Full particulars may be obtained from the Gas Council at 1 Grosvenor Place, London S.W.1.

[1] *Brit. med. J.*, 1956, 2, 1291.
[2] Ibid., *Suppl.*, 1956, 2, 201.

NEW CHIEF MEDICAL OFFICER

Sir John Charles, who has been Chief Medical Officer of the Ministry of Health and the Ministry of Education since 1950, is to retire on November 30, 1960. He will be succeeded by Dr. George Edward Godber, who became Deputy Chief Medical Officer at the Ministry on Sir John Charles's promotion to C.M.O. During his period of office Sir John has borne heavy responsibilities, fortified by wide experience, learning, imperturbability, and good humour. In 1950 the National Health Service had by no means got over its teething troubles, and the years since then have not been exactly serene. If relations between the Ministry and the medical profession have sometimes been strained, this has been none of Sir John's making, and he more than most must have been irked by the lack of money for much-needed hospital improvements. After twelve years as medical officer of health of Newcastle upon Tyne Sir John moved to the Ministry of Health in 1944. Since then he has been immersed in the development of Britain's Health Service, but has still found time to support the World Health Organization—he was president of the Twelfth World Health Assembly last year—and to seek inspiration from medical history in meeting the problems of the present day.

All Dr. George Godber's many friends in the medical profession will welcome his promotion and wish him well in the future. His carefully thought-out and well-balanced views have helped to keep the wheels of medical administration, whether local or national, running smoothly. Aged 52, he was educated at Bedford School, New College, Oxford, and the London Hospital. Two years after graduation he took the M.R.C.P. and entered the public health service, working with the London and Surrey County Councils. He joined the staff of the Ministry of Health in 1939 and became Deputy Chief Medical Officer in 1950. Six years before this he had taken part in the Ministry's massive survey of hospitals in Britain, being one of the inspectors of the Sheffield region. A Fellow and member of the council of the Royal College of Physicians, he is at present a member of the Working Party on Medical Staffing Structure in the Hospital Service, of which Sir Robert Platt is chairman.

BIOLOGY OF SPACE TRAVEL

[From a Special Correspondent]

Following shortly after the European Congress of Aviation Medicine,* the Symposium on the Biology of Space Travel, organized by the Institute of Biology at the Royal Geographical Society on September 29 and 30, proved an excellent opportunity for those interested in this fascinating field to extend their knowledge to include the highly topical problems of space flight.

Acceleration and Weightlessness

For the opening session Sir Lindor Brown, biological secretary of the Royal Society, took the chair. In the first paper, on the accelerations involved in leaving the earth and re-entering the atmosphere, Air Commodore W. K. Stewart, of the R.A.F. Institute of Aviation Medicine, Farnborough, gave an account of recent work at the Institute on acceleration. The relative dearth of information about the physiological effects of acceleration applied, he said, to the semi-recumbent astronaut, as opposed to the more erect-seated aviator. Apparently the accelerations involved in launching two- or three-staged rockets were tolerable, but a passenger could not be expected to carry out any movements other than of the supported hands. Re-entry loads were likely to be extremely fierce, but again tolerable. The influence of emotional stress upon acceleration tolerances were, however, virtually unstudied, and might be of great significance. Wing Commander T. C. D. Whiteside, also of Farnborough, followed with a lively communication on the effects of the gravity-free state which would be encountered by man in orbital flight. Clearly, early prognostication of profound disturbances was unwarranted, and the problems of locomotion within the very limited confines of a small space vehicle, and feeding, were probably readily soluble. However, muscular asthenia was likely unless the astronaut carried out regular exercise, and tolerance to re-entry deceleration might be reduced by a long period of weightlessness. Postural sense might be seriously disturbed in the absence of adequate visual clues.

Lieutenant-Colonel W. R. Turner, U.S.A.F., of the Aerospace Medical Laboratory, Ohio, presented a paper on the selection of the much-publicized seven U.S. astronauts. He described the formidable physical and psychological tests to which these men were subjected in order to select them from the surprisingly large number of candidates with the basic qualifications, which included 2,000 hours of piloting jet aircraft, a degree in engineering, and graduation from a test-pilot school. The tests included simulation of many of the aspects of the "Project Mercury" flight profile, such as exposure to noise, vibration, acceleration, isolation, and heat stress. Clearly motivation played an enormous part in the high performance of those selected. It is unfortunate that none of the published accounts of the astronaut selection programme has included the range of performance achieved by the group in any one test.

Survival in Space

After lunch the chair was taken by Sir Solly Zuckerman, F.R.S., and the problems of maintenance of life in space vehicles was the topic. Dr. D. McK. Kerslake read a paper by Flight-Lieutenant J. Billingham, of the Institute of Aviation Medicine, on the thermal stresses of space flight. He described the mechanism by which man was able to resist severe heat loads such as were anticipated during re-entry, and gave data from recent experiments with air-ventilated garments which were now far enough developed to protect a man for at least four hours in an environment at 125° C. It seemed that if his vehicle functioned correctly the astronaut was unlikely to encounter intolerable thermal conditions. Dr. N. W. Pirie, F.R.S., of the Rothamsted Experimental Station, Harpenden, gave an account of the metabolic requirements of man and stressed the need for developing means of reducing the weight of foodstuffs to be taken on a long space voyage. These included the recovery of water from sweat, breath, and urine and the regeneration of oxygen from exhaled carbon dioxide. Potassium tetroxide would probably be adequate for short voyages, but algae or allied organisms might be carried to harness solar energy for the same purpose on longer voyages, so long as the vehicle was within a reasonable distance from the sun. Finally, Dr. Pirie suggested that for really long voyages, either entirely new methods of providing energy to man must be developed or some form of anabiosis (the "crystallized astronaut") might be essential. Unfortunately, no data were given on the already remarkably successful closed ecological systems developed in the U.S.A. Mr. S. W. F. Hanson, of Armour and Company Ltd., London, presented the results of some of the current research on the problems of feeding space-travellers, firstly with liquids and pastes for short voyages, and secondly with freeze-dried meals for long journeys. He stressed the importance of palatability and referred to the unlikelihood of success in the proposed use of algae from closed ecological systems as a major dietary constituent. A film (unfortunately aimed at a very different kind of audience to that present) illustrated the problems of feeding in the presence of oxygen equipment and under conditions of weightlessness.

*See *British Medical Journal*, September 24, p. 934.

Radiation Hazards and Psychological Stresses

On the morning of the second day Sir Harrie Massey, F.R.S., took the chair. Dr. P. Alexander, of the Chester Beatty Research Institute, London, presented a consoling picture of the radiation hazards from cosmic rays and the Van Allen radiation belts, so far as acute radiation sickness was concerned. He dismissed the hazard of genetic and neoplastic changes as acceptable in that so small a population was at risk. The highly topical subject of the reaction of individuals to solitude and confinement was critically reviewed by Dr. R. Beech, of the Institute of Psychiatry, Maudsley Hospital, London. Although this paper covered the published research thoroughly, the audience was left in doubt as to the magnitude of this problem in space flight, and the possibility of finding effective means of combating the effects of isolation. Dr. W. Grey Walter, of the Burden Neurological Institute, Bristol, in his contribution on "the Human Brain in Space Time" gave a fascinating account of his current research on the establishment of conditioned reflexes in man, and showed how much individuals varied in this respect. He posed the difficult question of specifying the desirable characteristics for a space-traveller.

Contamination by Foreign Micro-organisms

The chairman for the final session was Dr. A. S. Parkes, F.R.S., and the first paper was given by Dr. P. H. A. Sneath, of the National Institute for Medical Research, Mill Hill. He dealt very ably with the question, so beloved by writers of science fiction, of the dangers of contaminating the earth or planets with foreign organisms. Recent work had shown that some terrestrial micro-organisms might be capable of survival and reproduction in the Martian atmosphere. Dr. Sneath described the difficulty of sterilizing a space vehicle, but left no doubt in the minds of his audience about the moral responsibility of those conducting space-research programmes to ensure that this was done. The problem of the carriage of contaminating organisms by the occupants of manned vehicles was not discussed. Turning to the chances of bringing back organisms from other planets, he suggested that it would be advisable to study the effects of material from such sources on the occupants of a closed ecology chamber before allowing contact between planetary souvenirs and the earth or its inhabitants. How one could be sure of destroying harmful organisms whose limits of viability were unknown was not clear.

Finally, Dr. Harlow Shapley, of the Harvard Observatory, U.S.A., took an entranced audience on a trip through

the Universe at break-neck speed, searching for conditions in which life, defined as "a self-replicating system of macromolecules," might have evolved. That such conditions existed in other solar systems he had no doubt, and the possibility of such within our own solar system could not be dismissed. This was particularly true if one would admit to the possibility of life based on an element other than carbon. Recent work had shown that the passage of electrical discharges through a simulated primeval atmosphere could produce amino-acids. A member of the audience pointed out that the steps between amino-acids and nucleic acids were a large gap in any hypothesis on the origin of living matter from inorganic materials.

Conclusions

The symposium as a whole was refreshing in that it brought together a wide range of biologists, engineers, and physicists and so allowed a reasonably rational assessment of the possibilities of successful, manned, space-flight to be made. It seems that the problems of ballistic and short orbital flights are not unsurmountable, given reliable vehicles. Obviously the question of true space travel is less readily solved, although many of the problems are not beyond the ingenuity of scientists. The principal gap in our knowledge is the absence of first-hand information on the conditions to be encountered. Have we omitted any vital factors from our assessment of the risks? Are the first astronauts going to encounter hazards which have not been considered as serious? Only when this is known as a result of exploratory flights can the chance of true interplanetary travel be assessed. It was a pity that no information was available to the symposium on the reaction of the animals in the recently announced successful orbiting flight and subsequent recovery of a large "sputnik." It seemed inevitable, also, but essential, that the usefulness of man exploring space should be raised, as it was by Sir HARRIE MASSEY. Nobody countered with the stock answer, "Because it's there," but some doubt obviously existed as to the value in scientific terms of putting man in an orbital vehicle except as a physiological experiment in order to assess the chances of true space travel. Whether the astronaut's ordeal will be conducive to reliability as an observer, and whether the selection techniques will prove to have been valid, must be established before interplanetary exploration can be planned.

ACCIDENT MANAGEMENT AND GENERAL PRACTICE

[FROM A SPECIAL CORRESPONDENT]

A joint symposium sponsored by the College of General Practitioners and the Institute of Accident Surgery and supported by the British Orthopaedic Association was held in Birmingham on September 24 and 25.

The first session on the "Accident Problem" was under the chairmanship of Mr. NORMAN CAPENER (Exeter).

Accidents in General Practice

Dr. R. M. MCGREGOR (Hawick) gave the practitioner's views with an epidemiological account of accidents in his practice over a period of 11½ years. In his semi-rural practice accidents accounted for 13% of all his work. Except in the elderly, accidents were commoner in men; over the age of 65 women were much more accident-prone. These sex differences existed in both town and country, but accidents as a whole tended to be more frequent in the towns. Most of the G.P.'s accident cases were minor and most occurred in the home, associated with housework. The 3,725 accidents in his series were responsible for 41,000 days of invalidism, 13,560 days of absence from school or work, and 5,360 days in hospital. He managed 97% of the accidents himself, only 111 out of 3,725 being referred to hospital.

Dr. McGregor showed that there was evidence for a steady increase in the number of accidents each year, and each year the peaks occurred in the summer months. He postulated that there was a definite group of individuals who were "accident-prone," and in general practice these people also had higher than average sickness rates. In general the highest rates were in young males and in elderly females. In many cases "accident proneness" was associated with fairly obvious preventable social factors.

Surgeon's Viewpoint

Mr. W. GISSANE (Birmingham), in giving the surgeon's viewpoint, stated that accidents had been responsible, and still were responsible, for the first epidemic in the history of surgery. The increasing numbers were related to development of motor power and to the great popularity of sporting activities. The present accident problem went well beyond surgical techniques and involved the whole of the medical profession. We must all play our parts in the prevention of the disease of accidents. It was estimated in 1951 that more than 500,000 minor wounds were occurring daily. At that time it was also discovered that 30% of wounds in industry were becoming infected, with much loss of time. Since then by a process of notification and more skilled treatment the infection rate had fallen by 200%.

In discussing the role of the hospital, he stressed the great importance of early treatment. In serious accident it was a matter of life and death; delay of an hour or two might make all the difference. He referred to Colebrook's work, which had shown that the longer wounds and burns were uncovered the greater the risks of infection. At present the location and the planning of hospitals were quite unrealistic to meet the needs of accidents. Large central accident departments were needed to cope with the problem. He wanted to see more "general surgeons" trained specially to staff these departments, which would require all medical resources working as a closely knit team. A complete 24-hour co-ordinated service was necessary. There was much scope for preventing accidents, but it was only in industry, where the hostile environment could be controlled, that spectacular advances had been made. On the roads and in the homes simple and common-sense measures would do much to prevent accidents—for instance, better staircases and the enforcement of fire-prevention regulations. On the roads more careful research into practical preventive measures was needed.

Needs of Casualty Departments

Dr. W. N. LEAK (Cheshire), who opened the discussion, spoke of the economic and organizational needs for controlling the epidemic of accidents. Mr. J. C. SCOTT (Oxford) noted that in Oxford the numbers of fractures had increased sixfold since the war. A combined approach to the problem was necessary. More emphasis should be laid on the proper care of the so-called minor cases by the G.P.s. In casualty departments an adequately staffed 24-hour service was an essential, and adequate staff and premises must be planned for managing the really serious major injuries. Dr. LIONEL FRY (London) gave the casualty officer's views. Having acted as a casualty officer in a London teaching hospital, he concluded that it was not the major accident which presented the problems but the minor non-traumatic conditions. In the average "casualty" department only half of all the cases were actual casualties or emergencies; the remainder presented problems that were more in the G.P.'s field. The "casual attender" was a social problem. Improvements were required in the training and supervision of casualty staff by registrars or consultants.

G.P.–Hospital Integration

In the session on "Integration of Hospital and Practice Work" Dr. JOHN FRY (Beckenham) considered the problems of the G.P., the hospital, and the patient. Although 10% of all his work was in dealing with "accidents," most of these were of a relatively minor nature and the technical

problems of anaesthesia, surgical techniques, and sterility were readily overcome. In the G.P.'s relations with the casualty departments there was much room for improvement. On the one hand it was a fact that a small proportion of G.P.s tended to abuse this department, using it for quick access to other hospital departments, both out-patients and the wards, and to obtain a second opinion from a much junior colleague. This was obviously not a correct situation and must be remedied. On the other hand the G.P. rarely received information on those of his patients who did visit the casualty departments.

The problems facing the hospital were much greater. They had been considered in the recent report of the Nuffield Provincial Hospitals Trust *Casualty Services and Their Setting*.* This report, based on a survey of 20 hospitals serving 5 million people, considered that there was urgent need for action. It was found that premises were poor, as were the clinical techniques used; that in all hospitals there were acute problems in staffing; that there was only nominal consultant supervision; that there was no adequate voice for the department in the hospitals' committees; and that there was great apathy over the whole situation in the management committees.

The public's attitude to casualty departments was of some importance, continued Dr. Fry, because habits and customs tended to stick. In urban areas these departments had become almost alternatives to general practice. If their family doctor was unobtainable then the patients went at once to the hospital with their G.P. problem. The Nuffield study had found that in only 30% of the cases reviewed was there a condition requiring hospital attention, and it had also found that in 50–75% the patients attended "of their own volition." However, it would be quite wrong to close these departments to these patients unless it was certain that G.P.s could take over the task. The Nuffield Committee had made some practical suggestions that should be considered. In each area of the country teams of local doctors (including G.P.s) should carry out surveys on the departments to consider staffing, siting, and the role of the casualty department in accident management.

Administrative Problems

Dr. K. R. D. PORTER, of the Birmingham Regional Hospital Board, described the situation in his area. The problem was to provide a 24-hour service to care for the serious accidents. Four accident units were being formed—in Birmingham, Stoke, Coventry, and Wolverhampton. The Institute of Accident Surgery would be responsible for training the staffs. The Regional Board realized that the existing casualty departments were poor, but they were being improved. The career structure was a major difficulty. Junior staff were difficult to attract, and many had qualified abroad. The more senior casualty officers found the work unsatisfying. General practitioners were now staffing some of the casualty departments with great success, and it was intended to develop this further. The surgeon in charge of the department should be a general surgeon and there should be a general physician associated with the department. Plans had also been made for major disasters, and arrangements made for general practitioners to play their part in such eventuality on the spot.

Dr. JOHN H. HUNT (London) showed some slides of his recent visit to Russia to illustrate casualty services there. More than 75% of Russian doctors were women and all worked a 6½-hour day. There was much standardization of thought and equipment, and this applied also to the accident services. The organization for this was most impressive on a military level. Emergency services were organized to meet the demands of the home as well as of the roads and industry. Dr. R. COVE-SMITH (London) pointed out that the home was a most dangerous place, and he stressed the importance and the value of an adequate knowledge of first aid by the general public.

*See *Brit. med. J.*, September 24, p. 920.

Other Sessions

On September 25 two further sessions were held and their proceedings will be published. Dr. G. F. ABERCROMBIE (London) took the chair in a discussion on "Major Injuries" at which Dr. W. N. LEAK, Mr. P. S. LONDON, Dr. A. J. LAIDLAW, Mr. H. PROCTOR, Mr. L. W. PLEWES, Dr. R. F. L. LOGAN, Dr. F. V. A. BOSE, and Dr. S. SEVITT were speakers. Mr. W. GISSANE (Birmingham) was chairman at a session on "Burns and Minor Injuries" at which Dr. R. S. C. FERGUSSON, Dr. D. BIGLEY, Mr. T. G. LOWDEN, Dr. A. A. WHITE, Dr. J. P. BULL, Dr. J. W. HAUNAY, and Mr. J. S. CASON spoke.

FORENSIC PATHOLOGY AND MEDICINE

INTERNATIONAL MEETING IN NEW YORK

[FROM A SPECIAL CORRESPONDENT]

The second International Meeting on Forensic Pathology and Medicine was held in New York from September 18 to 21 under the auspices of the Department of Forensic Medicine, New York University Medical Center, and the Office of the Chief Medical Examiner of the City of New York. The first morning included the dedication of a new Chief Medical Examiner's office by ROBERT F. WAGNER, Mayor of the City of New York. The conference was attended by the largest body of forensic experts ever to gather together in the United States, and included representatives from 40 countries. More than twenty were from the United Kingdom.

Post-mortem Bruises and Skeletal Remains

Dr. F. E. CAMPS was chairman of the first general session, which included a paper by Professor C. J. POLSON (Leeds) entitled "Post-mortem Bruising." Professor Polson pointed out that, although there was general agreement that post-mortem bruising rarely gave rise to difficulties in interpretation, there could indeed be confusion if the bruises were small. Although the shape of a bruise might closely correspond with the weapon or other bruising agent if death ensued shortly after the injury, it must not be assumed that just because the bruise showed a clear pattern the bruise had been inflicted shortly before death. Theoretically, even if survival after bruising was only a matter of minutes, the continuing circulation should cause escape of blood from damaged vessels so as to blur the pattern. In practice, however, clear bruising of a fresh colour might persist for hours after death.

Dr. W. M. KROGMAN (U.S.A.) read a paper on "The Reliability of the Identification of Human Skeletal Remains." In determining their age, he said, an accuracy of plus or minus one year was reasonable up to 20 years of age. Over 20 the endocranial sutures might be studied, but they were reliable only within a decade. The pubic symphysis was the most reliable (within five years), and if other bones were available as well the accuracy might be reduced to one to two years (plus or minus). Up to about 15 years sexing of a skeleton was about 50% accurate, but if the pelvis were present there was a 75–80% degree of accuracy. In adult material the odds in favour of correct sexing were as follows (depending on whether the following were available for examination): entire skeleton, 100%; skull, 90%; pelvis, 95%; skull and pelvis, 98%; long bones, 80%; long bones and skull, 90–95%; long bones and pelvis, 95% plus. Dr. Krogman discussed ancillary aids such as microscopy of cancellous bone, blood typing from bone (which he regarded as unreliable), skull-head comparison with portraits, photographs, etc., and cephalometric

radiographs, which he considered of great value in establishing individuality, particularly in mass disasters. Dr. Krogman emphasized the paramount importance of recovering every fragment of bone for examination.

Investigation of Sudden Death

The second general session, on "Medico-legal Systems," was under the chairmanship of Dr. C. KEITH SIMPSON (London). It included a paper by the late Andrew Nixon, who was until his death procurator-fiscal of Aberdeen, entitled "The Scottish System of Investigating Sudden Deaths." His paper was read by Dr. J. A. IMRIE (Glasgow). In Scotland forensic post-mortem examinations were not carried out unless there was some reason for suspicion. If there was, the examination was made by two surgeons.

Dr. J. D. J. HAVARD (London) read a paper entitled "Comparative Systems of Investigation of Sudden and Unexplained Death" in which he contrasted the Continental, coroner, and medical examiner systems. He pointed out the dangers under the Continental system, where the investigation was normally limited to those deaths which gave rise to suspicion. Since the main purpose of a modern medico-legal investigative system was to expose grounds for suspicion, the system defeated its own purpose if it led to the examination of only those cases which already had given cause for suspicion. Comparing the percentage of medico-legal necropsies carried out on the total number of deaths under the various systems, he showed that the coroner system generally achieved a much higher percentage than did either of the other two systems. However, a high necropsy rate might be illusory unless the necropsies were competently carried out. Finally he questioned the advisability of overthrowing the coroner system in the United States and replacing it by medical examiner systems, as much that was good in the coroner system was lost in the process. He referred to the political barriers to reform of the coroner system in the United States, but suggested that those countries operating coroner systems efficiently should be studied before the coroner system was condemned out of hand.

Cot Deaths and Drowning

For the remainder of the meeting the papers were read in Sections. In the Section on Forensic Medicine and Toxicology, Dr. F. E. CAMPS (London) read a paper on "Unexpected Deaths in Infants" in which he discussed the experimental work of Coombs in Cambridge on animals. Amongst other things Coombs had succeeded in showing that reaction to milk could be produced experimentally in animals which closely resembled the necropsy findings in infants presumed to have died from mechanical asphyxia or infective processes. This work was being pursued and might well provide an answer to the problem which was posed by unexpected deaths in infants. Dr. D. G. RUSHTON (London) read a paper entitled "A Reassessment of the Evidence of Drowning," in which he discussed the giant paper section technique for ascertaining structural damage of the lungs and the significance of small amounts of immersion medium in the respiratory tract. He stressed the value of diatom studies in the recognition of drowning where the changes were atypical or the body decomposed.

Papers by other British contributors included one on "Alcohol and the Motorist," by Dr. T. BLENCH (Manchester). Dr. KEITH SIMPSON spoke on "The Use of the Medical Artist in Teaching Forensic Medicine," and his paper, illustrated by some most interesting slides, was one of the most enjoyable papers in the whole meeting. Dr. W. EVANS (London) read a paper entitled "Adipocere Formation in Relatively Dry Environment." Until the end of the second world war adipocere formation in human cadavers was thought to be relatively uncommon and to require extraneous water. However, in personally conducted exhumations of 109 human remains in which death had taken place between 100 and 200 years ago, Dr. Evans had found adipocere formation in more than half, although all had been inhumed in dry vaults.

Suicidal Hemisection

A large number of papers were read in the various Sections. One recorded a particularly grotesque suicide.

Dr. H. H. SWEETS (Missouri) described how a mentally disturbed man, aged 46, had dived under a slowly moving diesel engine, one wheel of which had severed his body transversely, exposing the periosteum of both iliac crests and pulling the sacrum out of the pelvis. One 105-lb. (48 kg.) portion consisted of the legs, perineum, hips, and pelvis without the sacrum, but with parts of the ureters and half of the urinary bladder. The other portion, about 75 lb. (34 kg.), was alive, conscious, and in no pain. The blood vessels were crushed shut by pressure and the blood volume of the remaining portion was unaltered. The man helped the rescuers, talked, sang, and signed a statement. Completion of the surgical repair of the open peritoneal cavity was carried out by two surgeons, but the man died of shock suddenly five and a half hours after the injury.

Scientific exhibits at the meeting included illustrations of investigations into sudden and unexpected deaths in infancy (Dr. F. E. Camps). Dr. CAMPS also presented Dr. MILTON HELPERN, the chief medical examiner of the City of New York, with a portrait subscribed to by the European members attending the conference, and Dr. KEITH SIMPSON presented Dr. HELPERN with a necropsy knife given by his friends at London University. Sir SYDNEY SMITH, who attended the meeting, was presented with a medal commemorating his outstanding contributions to forensic medicine. Social events included a reception by the Mayor of the City of New York in his private residence.

CHILD NEUROLOGY AND CEREBRAL PALSY

[FROM A SPECIAL CORRESPONDENT]

The Second International Study Group on Child Neurology and Cerebral Palsy, sponsored by the National Spastics Society, was held at St. Edmund Hall, Oxford, from September 11 to 17. It is interesting to look at the programme in the light of current attitudes to cerebral palsy. The meeting opened with papers on the motor function of the spinal cord by Professor J. D. FORTUYN, professor of neurology at Groningen, Holland, and Dr. J. A. V. BATES, of the M.R.C. Unit at the National Hospital, Queen Square. On the second day the study group moved over to Dr. L. Guttmann's Spinal Rehabilitation Unit at Stoke Mandeville, where spasticity in the motor disorders of the spinal cord and spina bifida cystica were discussed. Dr. DERMOD MACCARTHY pointed out that the latter was a common disorder, with an incidence of 1 in 400 births, and that proper help to these children and their families involved long-term planning and support. The choice of these subjects underlined the realization that cerebral palsy is but one item in the field of the neurology of infancy and childhood, not an isolated phenomenon. The session on neurochemistry cast further light on this broad approach to cerebral palsy. Drs. B. A. HAGBERG and SVENNERHOLM read a paper on metachromatic leucodystrophy, and Professor Y. CIZKOVA, of Prague, discussed the relation of the thyroid gland to the development of the central nervous system. The session concluded with papers on the regulation of metabolism, by Dr. D. RICHTER, of the M.R.C. Neuropsychiatric Research Unit, and on biochemical changes in the developing brain by Professor J. N. CUMINGS, of the National Hospital, Queen Square. These papers also emphasize the current interest in the early development of the foetal brain. For, while 50% of cases of cerebral palsy appear to be associated with perinatal

difficulties and perhaps another 10% are post-natal in origin, there remain some 40% which arise apparently during foetal life.

Early Diagnosis

At a full session on the neurological examination of the newborn, Drs. R. Mac Keith and P. E. Polani, of Guy's Hospital, Dr. R. S. Paine, of Boston, Mass., and Dr. H. F. R. Prechtl, of Groningen, discussed a circulated report of a meeting of the Little Club at Groningen in July, at which the various neurological tests were debated at length and an agreed description of how to do them and what responses to expect was drawn up. Dr. Prechtl, in a notable contribution, said he had found that a large proportion of neonates with abnormal neurological signs showed signs of neurological or behavioural disorder later in childhood. Professor R. S. Illingworth replied that, as we came to make more detailed neurological examinations of newborn infants, we should probably find abnormalities more often, and the assessment of their significance would require care. By no means all children with abnormal neurological signs in the neonatal period were going to have later disorder, and it was important not to assume this.

Early recognition of cases of cerebral palsy depends partly on following up infants which have been exposed to special risk, but also on a very close knowledge of development. Professor Illingworth, presenting a film of "developmental surprises," said that though some surprises occurred it was usually possible to give a reliable estimate of the child's future intellectual capacity by careful examination before the age of 6 months. In his own series his forecast had turned out to be right in 95% of cases. Also concerned with the problems of early diagnosis was a fascinating session on the possibilities of improving the perceptual skills of clinical examiners, which was addressed by Dr. M. L. Johnson Abercrombie, author of the recently published book *The Anatomy of Judgment*.

Disorders of Sensation

The methodology of assessing the results of treatment, an urgent problem, was studied in considerable detail. Dr. K. S. Holt, of Sheffield, described his method of analysing gaits. The study group also gave a day to the functions and disorders of the parietal lobe and the recognition of these by clinical examination. The disorders of sensation, other than those of hearing, which occur in cerebral palsy were discussed by Dr. Marit Skadvedt, of Oslo, who emphasized that it was very common, indeed usual, for the cerebral-palsied to have more than one disorder and that disorders of sensation were common, and by Dr. R. S. Paine and Dr. J. P. M. Tizard, who discussed the disorders of sensation found in the hemiplegic limb. A further session was devoted to the perceptual disorders in cerebral-palsied children; disorders of body image; disorders causing dyslexia and dysgraphia; defects of spatial perception in children, and (by Dr. Guy Tardieu, of Paris) defects in recognition of forms by the hand, ending with a masterly survey of the problems of perceptual disorders in cerebral palsy by Professor O. Zangwill, professor of psychology at Cambridge.

The American Degree: a Comparative Study for British Students, by Bernard Mellor, registrar of Hong Kong University, has been published recently by the University Presses of Hong Kong and Oxford. A section on medicine is included, but those who want to study medicine in the United States are warned: "While medicine is the subject of popular aspiration among Commonwealth students in America, admission of foreigners to American medical schools is rare. At least 40 of the 78 approved schools are no longer accepting foreigners, of whom there are less than 500 in a total enrolment of over 28,000." (Price: in Hong Kong, H.K.$2.50; abroad, 3s. 9d. or U.S.$0.60. Obtainable in the United Kingdom from O.U.P., Amen House, Warwick Square, London E.C.4.)

Nova et Vetera

HISTORY OF MEDICAL PRACTICE IN BRITAIN

The First British Congress on the History of Medicine and Pharmacy, held in London last week, had as its chosen theme "The Evolution of Medical Practice in Britain." Organized by the Faculty of the History of Medicine of the Society of Apothecaries and sponsored by the Wellcome Foundation, the meeting could have had no more appropriate topic for its discussions. It was the "apothecary" who was the general practitioner of the eighteenth century, and it was the "new young men," examined and licensed by the Society after the Apothecaries' Act of 1815, who swelled the ranks of the medical reform movement which led to the British Medical Association. The new Faculty, as its chairman, Dr. W. S. C. Copeman, said in his presidential address, was founded to provide common ground for all (institutions and individuals) who regard the history of medicine as a study enriching every department of medical thought and action. He also emphasized the value of history in exposing the origins of unsolved problems and of social and professional beliefs and attitudes which still influence the modern approach to their solution.

All the speakers at the congress drew from their own specialized studies to show how medical practice in Britain has been created and shaped into the form we know to-day. In the opening paper, Dr. F. N. L. Poynter discussed Government legislation for the profession, from the first abortive petition of 1421 to the Consolidated Medical Act of 1956, and the point was well made that the inspiration for it throughout was almost entirely of professional origin. It was not a case of a backward profession being dragooned by an enlightened Government, but too often of a reluctant Government conceding to a profession the legislative support it demanded for its own improvement. Dr. Charles Newman, in assessing the influence of medical education, showed how practice is shaped by the beliefs held by doctors and how, at all periods, it has been kept at a high level by the influence of example.

The balance was nicely struck between the role of purely professional societies, especially in the nineteenth century, described by Dr. W. H. McMenemy, and patients' clubs and societies founded at the same time to provide medical care for special groups and classes. These, as Dr. Ffrangcon Roberts showed, had a powerful influence on general practice and helped to create the social climate for the National Health Insurance Act of 1911.

The influence of the Royal College of Physicians has been all-pervasive, and Sir Charles Dodds dwelt on its positive achievements as illustrated by the long reign of the *Pharmacopoeia Londinensis* and the introduction of inoculation and vaccination and the Boards of Health, as well as by the outstanding work of many of its individual Fellows. Sir Zachary Cope showed how the Royal College of Surgeons won its modern prestige by its ever-widening activities in surgical teaching and research and how that prestige had extended its influence over practice not only in Britain but throughout the Commonwealth and in many foreign countries. A similar view was presented by Mr. H. J. Malkin of the influence of the Royal College of Obstetricians and Gynaecologists.

In a thoughtful paper on the influence of clinical research on practice, Dr. K. D. Keele described the reception of several important discoveries and showed that their impact on practice had often been too long delayed, and Mr. Michael Perrin discussed the influence of the pharmaceutical industry on medical practice, emphasizing that the industry was essentially the product of the modern scientific revolution and had now become one of the chief agents for its further development. Not only had it transformed the routine work of the practitioner but it had also become the indispensable ally of the profession and Government in safeguarding and promoting the health of the people.

(*Continued at foot of next page*)

To-day's Drugs

Ferrous Fumarate

"Fersamal" (Glaxo).

Chemistry.—This is a ferrous salt of fumaric acid (ethylene-1:2-dicarboxylic acid), a very stable, reddish-brown, almost tasteless, microcrystalline powder containing 32.5% of ferrous iron, as compared with 31% in exsiccated ferrous sulphate. It is not readily oxidized in air, and can be put up in uncoated tablets.

Pharmacology.—Ferrous fumarate is quickly absorbed in the alimentary tract and utilized effectively—the haemoglobin increases being well within the expected range of response.

Therapy.—The preparation is intended for the prophylaxis and treatment of iron-deficiency anaemias in adults and infants, in whom effective haematological responses are obtained. It is available in (*a*) uncoated tablets of 200 mg. and (*b*) a sweetened aqueous suspension containing 100 mg. in each teaspoonful (3.5 ml.). The recommended effective dosage for adults is 1 tablet (200 mg.) or 7 ml. of the syrup three times daily, but double these doses can be given and are well tolerated. For infants it is ¼–1 teaspoonful (1.75–3.5 ml. containing 50–100 mg.) three times daily.

Side-effects.—Ferrous fumarate is usually well tolerated orally, and does not produce gastric or intestinal disturbances quite so frequently as many other oral iron preparations. Nevertheless, at least 4% of patients are reported to have mild or severe gastro-intestinal symptoms, sometimes with severe sickness, though very few have had to discontinue its use on this account. Because of the low incidence of side-effects it is said to be particularly suitable and safe for administration to infants. Some patients have complained of mild constipation.

Contraindications.—None, but an occasional patient may have to discontinue its use on account of very severe gastro-intestinal irritation and nausea.

N.H.S. Basic Price.—100 tabs., 3s. 1½d.; 6 fl. oz., 4s. 4½d.

(*Continued from previous page*)

Since the establishment of the National Health Service in 1948 historians in Britain have begun to appreciate the fact that the organization of medical care in any society is an important index of social and economic progress and that the present Health Service is the product of a long evolutionary process in which the medical profession has been vitally concerned. The various stages in this process need much closer study, but the papers read at the Congress went some way towards mapping out the field. How usefully the mainly "iatrocentric" views expressed in them may be complemented by those of the general historian was illustrated by Mr. PETER LASLETT'S account of patient and doctor in pre-industrial England, when women provided much of the attention needed by the sick. Dr. R. M. S. MCCONAGHEY, speaking for the College of General Practitioners on the history of rural practice, said that when England was a predominantly agricultural country the people, despite their long attachment to folklore, had their well-trained and highly respected practitioners for long periods; it was easier in their small communities to protect the public from the unlicensed quack than it was in the large towns and cities. It was appropriate, too, at this first British Congress, to hear Dr. DOUGLAS GUTHRIE, speaking for the Scottish Society of the History of Medicine, emphasize the important influence of Scotland upon the evolution of medical practice in Britain. Its Royal Colleges, its universities (especially its celebrated Edinburgh Medical School), and its doctors have all played a more than proportionate part in making British medicine what it is to-day.

In his address at the Congress Dinner, Lord COHEN OF BIRKENHEAD spoke on the uses of medical history, and the stimulating and thoughtful papers presented during the meeting (and to be published in volume form) bore witness to the strength of his arguments.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Faulty Anaesthetic Apparatus

SIR,—The following unnerving experience may be of interest to those called upon to administer dental or other anaesthetics. Shortly after returning from holiday I was asked to anaesthetize a child in one of the local hospitals for the extraction of some teeth. The apparatus in use in the dental clinic of this hospital is a well-known and reliable intermittent positive-pressure machine which has given excellent service during the past 11 years, and which was in normal working order on the last occasion it had been used. During the induction the regulator was adjusted to give 10% of oxygen; but, instead of this having the desired effect, I was suddenly and unexpectedly confronted with an acute anoxic crisis which nearly resulted in the death of the patient. More or less the same thing happened to the next patient, who happened to be the sister of the previous child, but, having been forewarned, greater caution was observed and the anaesthesia was completed without untoward incident. Suspecting a fault in the apparatus, a rough test was carried out which showed that apparently no oxygen emerged from the machine until the regulator was turned to about 12% as indicated on the dial.

On making further inquiries it transpired that during my absence on holiday the apparatus had been dismantled and "serviced," not by the manufacturer's agents, but by the service mechanic of another company. I at once ordered the apparatus to be sent for examination and testing at the official manufacturer's depot, and in due course their report was sent to the effect that "an excessive amount of grease had been placed upon the mixing key, thus obstructing the free flow of oxygen through the oxygen port, causing the mixtures of nitrous oxide and oxygen to be extremely inaccurate."

As this sort of accident can happen to any form of nitrous oxide and oxygen machine where the anaesthetist has to rely on a calibrated dial or regulator, it would be unfair to mention the name of this particular apparatus, which has a world-wide reputation for reliability and long service. My object in reporting this mishap—which might easily have resulted in a fatality—is to draw attention to the unsatisfactory conditions under which routine servicing of anaesthetic apparatus is often carried out, and it is time that more stringent regulations were enforced by hospital authorities. Whenever possible, routine service and overhaul should be carried out only by the manufacturers or their agents, and a certificate issued stating that the apparatus is in proper working order within reasonable limits of accuracy. As a constructive suggestion, "reasonable accuracy" might be defined as complete accuracy between 0 and 10% of oxygen, and not more than 1% error between 10% and 20% of oxygen; greater accuracy would probably not be practicable in most of the anaesthetic machines available at the present time.

These rules should also be applied when new apparatus or pipe-lines are to be installed: at present such contracts are frequently given to outside firms with little or no knowledge of anaesthetic requirements, presumably because it costs more to have the job done

by the reputable and experienced anaesthetic firms who have given such excellent service to hospital anaesthetic departments in the past.—I am, etc.,

Newcastle upon Tyne. PHILIP AYRE.

"Celbenin"-resistant Staphylococci

SIR,—Dr. Mary Barber's letter on "celbenin" (September 24, p. 939) is in some ways misleading. She is right to draw attention as others have done[1,2] both to the fact that laboratory cultures of staphylococci *can* develop resistance to celbenin and to the fact that ultimately resistance *could* become a clinical problem. She is right again in urging that every possible care should be taken, by using the drug discreetly, to reduce the chances of clinical resistance arising. But it is essential to separate present facts from fears for the future. So far clinical resistance to celbenin in staphylococcal infections has not been reported, and out of a large number of strains of *Staphylococcus pyogenes* isolated from clinical material none so far has proved resistant to celbenin. As Dr. Barber herself says, the proof of the pudding is in the eating, and it seems premature at this stage to dwell on the hypothetical effects which may occur in the future as a result of over-indulgence rather than on the undoubted fact that the pudding itself seems to be a very good one for which we should be truly thankful.

Dr. Barber remarks that it is fortunate that the drug is expensive and unsuitable for oral administration and is therefore likely to be used with discretion. This surely is a somewhat defeatist attitude. If a drug is a good one, then it should be used when properly indicated, and rationing by price or because it is to be given by injection is not a good way of controlling its use. Most doctors would prefer to give, and surely all patients would prefer to receive, an effective oral drug if such were available rather than repeated injections which may be painful. An effective oral preparation of celbenin, if it were available, may be welcomed rather than feared. Some recent figures[3] show that there were many anaphylactoid reactions following intramuscular injections of penicillin and that around 10% of these were fatal, while no deaths occurred in anaphylactoid reactions following oral penicillin.—I am, etc.,

Department of Bacteriology,
Guy's Hospital Medical School,
London S.E.1. ROBERT KNOX.

REFERENCES

1 Rolinson, G. N., Stevens, S., Batchelor, F. R., Ward, J. C., and Chain, E. B., *Lancet*, 1960, 2, 564.
2 *Brit. med. J.*, 1960, 2, 687–709.
3 Welch, H., Lewis, C. N., Einstein, H. I., and Boeckman, B. B., *Antibiot. Ann., 1957–8*, 1958. Medical Encyclopedia Inc., New York.

SIR,—I am sure that the note of caution sounded by Dr. Mary Barber in her letter (September 24, p. 939) is a wise one. It is in fact the same note of caution which most of us tried to ring before, as well as in, our publications of September 3 (pp. 687–709). There are, however, some points in her letter which should be answered. Surely the promise of "celbenin" derives only in part from its comparative immunity to penicillinase; the major consideration is that, at present, all strains of *Staph. aureus* are uniformly sensitive to it. This was never the case with penicillin G, for, even in 1944, one encountered strains, unexposed to the drug, which were resistant to 5–25 units/ml.[1]

I am not surprised to learn that, after repeated passages, Dr. Barber has been able to induce resistance *in vitro* to two strains of *Staph. aureus*. A similar result was mentioned in two of the publications on September 3, and by Rolinson *et al.* on September 10.[2] In my hands, *Staph. aureus* is slow to acquire resistance to celbenin even *in vitro*, and in this hospital, where more than 60 cases have now been treated, there is no evidence to date of resistance *in vivo*. As far as I can see at the moment the danger lies rather with ubiquitous commensal *Staph. albus*, which acquires resistance *in vitro* to over 1,000 μg./ml. with remarkable speed, and can also acquire some resistance, of a lower order, *in vivo*. I entirely agree therefore with Dr. Barber that the mechanism of resistance—as well as the mode of action—of the new compound is different from that of penicillin G.

Time alone will tell us the true value of the new forms of penicillin, and there are undoubtedly grounds for caution in the use, as well as in the assessment, of celbenin. Nevertheless the new drug is more eligible than most for immediate use in severe staphylococcal infections, especially when, as in hospital-acquired infections, there is a possibility of resistance to natural forms of penicillin and other antibiotics.—I am, etc.,

Queen Mary's Hospital for Children,
Carshalton. G. T. STEWART.

REFERENCES

1 Stewart, G. T., *Lancet*, 1945, 2, 705.
2 Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron-Wood, J., and Chain, E. B., ibid., 1960, 2, 564.

Mode of Action of "Celbenin"

SIR,—Dr. Mary Barber's letter (September 24, p. 939) raises the question as to whether the mode of action of "celbenin" and penicillin G might be different.

It is now well established that at least one of the ways in which the natural penicillins exert their antibacterial effect is by preventing the synthesis of a rigid component of the cell wall. When Gram-negative bacteria are treated with penicillin G in hypertonic medium containing a source of Mg^{++} ions, aberrant forms or spherical forms (the so-called spheroplasts) are obtained depending on penicillin concentration. The latter undergo lysis by osmotic explosion when the tonicity of the environment is reduced. We have found that celbenin will induce spheroplast formation in *Proteus vulgaris*, *Chromobacterium prodigiosum*, and *Cloaca cloacae* at, respectively, 1, 25, and 60 times the inducing concentrations of penicillin G. The majority of these spheroplasts lyse on dilution with water. Concentrations of celbenin corresponding to 50, 40, and 40 times the spheroplast-inducing concentrations of penicillin G yielded mainly aberrant forms with but few spheroplasts in, respectively, *Escherichia coli* formerly NCTC 5934, *E. coli* strain K.12, and *Pseudomonas hydrophilia*. There is thus evidence of at least one common cytotoxic activity shared by penicillin G and celbenin, although the latter appears to be generally far less active in this respect.—We are, etc.,

Pharmacy Department,
University of Nottingham. W. B. HUGO.
A. D. RUSSELL.

Metronidazole in Trichomoniasis

SIR,—Gynaecologists as well as venereologists will be delighted by the enthusiastic reports of treatment of trichomoniasis with metronidazole, especially in view of the disappointing results of treatment with aminitrazole a few years ago. The three articles (September 24, pp. 902, 906, and 910) and your editorial comment

(p. 922) refer to the treatment of routine cases in which no particular complication was anticipated, and they lay stress on reinfection as the chief problem in recurrent cases. I wish to draw attention to the value of metronidazole in cases of trichomonal infestation of the vagina which have proved altogether resistant to local therapy, and in which reinfection is unlikely to have taken place. Two such patients have recently been cured (apparently) by this oral therapy after three and three and a half years respectively of almost uninterrupted and largely unavailing local treatment.

A single woman, aged 36, was found to have trichomoniasis of the vagina immediately following hysterectomy. She was treated successively with the following: "penotrane" pessaries, acetarsol pessaries inserted through a speculum, vaginal swabbing and packs, "aroxine" pessaries, "floraquin" pessaries, "penotrane" cream, further packs as an in-patient, floraquin pessaries (4 nightly), tampons, oestrogen, penotrane detergent swabbing, carbarsone pessaries, "sterisil" jelly, carbarsone (double dosage), "iodevan" swabbing, acetarsol pessaries, surgical toilet, "aci-jel" jelly, "triple sulfa cream," "dequadin" pessaries, "terramycin" pessaries, proflavine pessaries and mercurochrome swabbing. She worked as an orderly in hospital and swabs were sent regularly for laboratory examination, but although some forms of treatment gave temporary symptomatic improvement the trichomonads never disappeared from the vagina. Eventually metronidazole was used, 200 mg. being taken orally thrice daily for 14 days (double the recommended course), and, although the patient was reluctant to admit much benefit, the vaginal discharge showed only a few scanty trichomonal organisms. In view of the chronicity of the infection a further course of 200 mg. t.d.s. was given for three more weeks with the use of acetarsol vaginal pessaries as well. Relief was immediate and swabs have remained negative for two months.

The other patient was aged 25 when seen with a vaginitis that occurred during her third puerperium, and which commenced as a mixed infection of monilia and trichomonads. She was treated unsuccessfully with 14 different types of vaginal therapy, and a course of oral aminitrazole. Reinfection could not be entirely excluded, but seemed highly improbable. Temporary benefit occurred after the use of carbarsone pessaries and also after swabbing twice weekly with 10% mercurochrome. In view of the chronicity of the infection she was given a double course of metronidazole (200 mg. t.d.s. for 14 days), and was apparently cured. It is too early to exclude relapse, but the response was dramatic.

It is worthy of note that the first of these patients had been regarded as a psychiatric problem in view of her unsatisfactory emotional state, and it had been questioned more than once whether she did, in fact, wish to be cured of her vaginal discharge. The dramatic improvement in personality as soon as she found herself free from discharge for the first time in almost four years made her attendants realize how much emotional distress may be caused by chronic vaginitis.

The metronidazole ("flagyl") was very kindly supplied by Dr. R. Forgan, of Messrs. May and Baker Ltd.

—I am, etc.,

Birmingham. WILFRID MILLS.

New Rashes for Old

SIR,—We have just had a localized epidemic in this practice of the febrile illness and rash described by Dr. Joan B. Landsman and her colleagues (August 6, p. 464) and by Dr. J. Parton (August 27, p. 665). Seventeen children were affected and five of their parents, all living on the same housing estate. The rash was blotchy, pink, and papular on the face, maculopapular and suggestive of measles or rubella on the body. A third element, a transient confluent erythema in the groin, was noted in two cases.

One boy got virus meningitis on the fifth day, which first suggested that we might be dealing with the same illness as Dr. Landsman. All the others recovered within a week, the rash lasting between one and four days. Of the five parents affected, only one had the rash, the others complaining of sore throat, headache, and aching in the back and limbs, "like 'flu." The older children complained of sore throat and headache, while the younger were fretful with vomiting and loose stools. Two young children had cough and coryza, in one severe enough to suggest measles.

The Newcastle Virus Laboratory has isolated E.C.H.O. virus type 9 from the stools of five of the cases, including the boy with meningitis and two of the parents who had the illness without the rash.—We are, etc.,

ANDREW SMITH.
DEREK BELL.
DAVID F. SMITH.
MICHAEL BELL.

Newcastle upon Tyne.

Potassium Perchlorate in Thyrotoxicosis

SIR,—Your thoughtful leading article on potassium perchlorate in thyrotoxicosis (August 13, p. 517) mentions but does not perhaps sufficiently stress the rather remarkable relationship between the dose of this drug and the incidence of side-effects. This relationship emerged very clearly from the studies of Crooks and Wayne[1] in Glasgow. A recent review of our own patients shows that the incidence of all types of side-effects (taken together) is astonishingly similar in their clinic and ours, not only with potassium perchlorate but also with two other antithyroid drugs. The actual figures are given below:

Drug	Dose	Crooks and Wayne		Morgans and Trotter	
	mg./Day	No. of Patients	Toxic Reactions (%)	No. of Patients	Toxic Reactions (%)
Potassium perchlorate	400–1,000	200	2	180	3
Potassium perchlorate	1,200–2,000	50	16	67	18
Carbimazole ..	20–60	85	8	57	10
Methyl thiouracil	200–600	151	7	358	9

The close correspondence between the Glasgow and London series enables them to be combined for significance tests. These show that the smaller doses of perchlorate were associated with fewer toxic reactions than carbimazole or methyl thiouracil; whereas the larger doses of perchlorate were associated with more frequent toxic reaction than methyl thiouracil ($P<0.01$ in all cases). By the same criterion, large doses of perchlorate caused more reactions than small doses of perchlorate in both series, considered separately.

The 12 reactions in our patients treated with the larger doses (1,200 or 1,600 mg. daily) of perchlorate consisted of two cases of rash with fever, eight cases of rash alone, and two cases of lymphadenopathy. These are similar in type to the reactions observed by Crooks and Wayne, and can be regarded as manifestations of hypersensitivity. If reactions of this type are thought of as responses to a drug-protein complex which is acting as an antigen, the following

hypothesis may be put forward as a possible explanation of the marked relationship between the incidence of reactions and the dose of perchlorate. Let us suppose that perchlorate may become attached to one or both of two possible binding-sites within the body. One of these (A) has a greater binding affinity for perchlorate, and the complex formed is non-antigenic. The other (B), with a lesser affinity, only binds perchlorate when the capacity of the first binding-site is saturated. Perchlorate will only become bound to B when large doses are given, or in individuals with a reduced amount of A-type binding-sites. Only when perchlorate is attached to B is the resulting complex antigenic.

Whatever the theoretical explanation, it would seem advisable to take note of the close dependence of toxic reactions upon perchlorate dosage. It is likely that the only serious toxic effect—agranulocytosis—would be equally dependent upon dosage. Fortunately the instances of this complication so far reported are too few in number for direct verification of this supposition. Crooks and Wayne's case[1] was receiving 1,500 mg. daily, and Southwell and Randall's case[2] 1,000 mg. daily. To these we can add a third (unpublished) case seen by Dr. Harold Lambert at this hospital, in which a woman developed a severe leucopenia within two weeks of starting perchlorate in a dose of 1,600 mg. daily (this patient is not included in our series).

Our own previously published recommendations about perchlorate dosage are now seen to have been consistently wrong. In 1954 we were using 400 mg. daily,[3] a dose which is clearly too small to be effective in many cases. In 1957 we increased the dose to 1,600 mg. daily,[4] with the result that we are now able to confirm Crooks and Wayne's finding that doses of this order are highly toxic. A reasonable compromise would therefore seem to be to use doses in the region of 800 mg. daily.—We are, etc.,

M. E. MORGANS.
W. R. TROTTER.

University College Hospital Medical School, London W.C.1.

REFERENCES

1 Crooks, J., and Wayne, E. J., *Lancet*, 1960, 1, 401.
2 Southwell, N., and Randall, K., ibid., 1960, 1, 653.
3 Morgans, M. E., and Trotter, W. R., ibid., 1954, 1, 749.
4 —— —— ibid., 1957, 2, 1173.

Hypophysectomy in Breast Cancer

SIR,—Mr. M. A. Falconer and Mr. J. L. Hayward in a recent letter (September 17, p. 856) ask me to give the evidence on which certain statements in my Oliver-Sharpey Lectures are based. Briefly they may be summarized as follows:

(1) "That it is doubtful whether it is justified to undertake surgical hypophysectomy in patients with advanced breast cancer."

(*a*) It involves a major operation on a patient who has often had a major operation shortly before. Nearly all patients dislike the idea of a craniotomy. (*b*) The operation is not a cure, only 50% of patients can anticipate a temporary remission perhaps lasting one to two years. (*c*) Psychological changes may follow surgical hypophysectomy. (*d*) Diabetes insipidus developed in about half our cases and has lasted up to three years. (*e*) As Atkins *et al.*[1] point out, widespread introduction of surgical hypophysectomy for advanced breast cancer is impracticable in terms of neurosurgical man hours.

(2) That yttrium-90 implantation seems to have advantages over surgical hypophysectomy and bilateral adrenalectomy and that the Glasgow screw-in method is the best so far developed.

(*a*) It is a relatively minor procedure. (*b*) It is an effective method of pituitary destruction (Section of Endocrinology, Royal Society of Medicine. Discussion on the assessment of endocrine function after hypophysectomy or pituitary destruction, October 28, 1959). (*c*) It is relatively free from side-effects—the figure of 10% quoted by Mr. Falconer and Mr. Hayward for C.S.F. rhinorrhoea is incorrect; with the latest reported method it is 1 in 43.[2]

(3) Replacement therapy after adrenalectomy is undoubtedly simpler than after hypophysectomy.

After hypophysectomy not only must cortisone or a similar steroid be given but also thyroid replacement and in about 50% of cases pitressin. We have not found the snuff very satisfactory, and usually intramuscular injections of pitressin tannate in oil are required. The diabetes insipidus has given our hypophysectomized patients a lot of trouble. It should perhaps be mentioned that Mr. Valentine Logue, the neurosurgeon who performed these operations, has not clipped or coagulated the pituitary stalk. It has been cleanly divided.

—I am, etc.,

London W.1. JOHN NABARRO.

REFERENCES

1 Atkins, H. J. B., Falconer, M. A., Hayward, J. L., MacLean, K. S., Schurr, P. H., and Armitage, P., *Lancet*, 1960, 1, 1148.
2 Section of Endocrinology, Royal Society of Medicine, *Proc. roy. Soc. Med.*, 1960, 53, 81.
3 Forrest, A. P. M., Blair, D. W., Valentine, J. M., and Sandison, A. T., *Lancet*, 1959, 2, 971.

Medical Practice Centre

SIR,—Your Special Hospital Number (September 10) prompts me to cry out the needs of the Cinderella of the profession—general practice—which I cannot remember being given so generous a coverage.

To state the obvious: The practitioner's aim is to make the patient feel "at home" while devoting as much time and careful attention as possible to the history and examination, and then to the giving of advice. Unfortunately the interruptions of the telephone, the agony of waiting for an unwell person to undress and dress, while aware of a full waiting-room, inefficient filing systems, and so forth, can make us fall far short of our aim. Indeed, many efficiency factors enter into general practice—layout of accommodation, employment of ancillary help, types of furniture and equipment, to mention a few—which have no relation to the medical curriculum. One frequently finds that ex-trainees have not been recommended books on these matters, although there exists, for example, the Nuffield report *Good General Practice* by Lord Taylor.[1]

I feel there should be set up a Medical Practice Centre, which can advise on organization and methods in general practice. It should have a wide remit; its information be as well indexed as that of the Design Centre; the frequently changing exhibitions as comprehensive as those of the Building Centre. There should be peripatetic advisers, as offered, for example, by the Medical Insurance Agency, and the whole should be administered by the profession. To finance such a scheme on a realistic scale would require large capital, and perhaps one of the Trust Funds would be willing to help. Such a centre would assist us in raising our standards and would enable us to provide the best possible general medical service to the public.—I am, etc.,

London N.W.3. R. LAW.

REFERENCE

1 Taylor, S., *Good General Practice*, 1954. Oxford Univ. Press, London.

Our Hospitals

Sir,—While exciting plans are made for near-perfect hospitals of the future, may I draw attention to a comparatively inexpensive improvement which is urgently needed by existing hospitals? That is: the provision of adequate, modern, and clean bathrooms and lavatories.

In my days as a hospital resident the only interest taken in these rooms by the medical staff was to store oxygen cylinders and the like in the bathroom, and to avoid the patients' lavatory in favour of one marked "staff." As a patient I have had a closer view. I have been an in-patient in maternity, gynaecological, and surgical wards of hospitals, including a famous teaching hospital in a very old building, an equally famous teaching hospital in a modern building, an old provincial hospital, and a new wing of a provincial hospital. In all the medical and nursing care was of a high standard, but in all, without exception, the bathrooms and lavatories were inadequate in number and to a greater or lesser degree *dirty*. In addition, in the old buildings the wash-basins and baths were cracked and lacking in glaze, lavatory-seats were wooden and scrubbed until the surface resembled nutmeg graters, and large pieces of plaster were missing from the walls. In one maternity unit the charwoman's filthy brooms were propped, head-end up, in the corner of the w.c. In none of the hospitals was there any attempt to clean the bath or lavatory-seat between patients, although some provided a mop in a jar of soap solution for the patients to use on the bath. In maternity units where early ambulation is the rule the numbers of both baths and lavatories have become inadequate. It is usually necessary to queue for both.

What these conditions mean in terms of distress to fastidious patients is bad enough; what they must mean in terms of cross-infection is quite appalling. What is the point of using aseptic technique on the wards when obstetric and gynaecological patients are then going to get up and use uncleaned communal baths and lavatory-seats? The remedies are simple and not very expensive. (1) Cleaning of bathrooms and lavatories should not be done by the least intelligent "cleaner" but by a member of the nursing staff under the supervision of the sister. (Bedpans are always sterilized by nurses.) Some means should be devised for cleaning w.c. seats after each use. (2) All worn-out fittings should be replaced and the rooms kept in a good state of decoration. (3) Where necessary additional facilities should be provided even if other amenities or even bed-space have to be sacrificed. Above all, senior nursing and medical staff must be convinced of the importance of providing a standard of hygiene at least equal to that we enjoy in our own homes.—I am, etc.,

Rustington, Sussex. E. M. Arbuthnot.

Central Sterile Supply Departments

Sir,—The article on "Hospital Central Sterile Supply Departments," by Dr. V. D. Allison (September 10, p. 772), makes it apposite to note this paragraph in the *Hospital Building Builetin: Operating Theatre Suites, 1958*, page 61, paragraph 352:

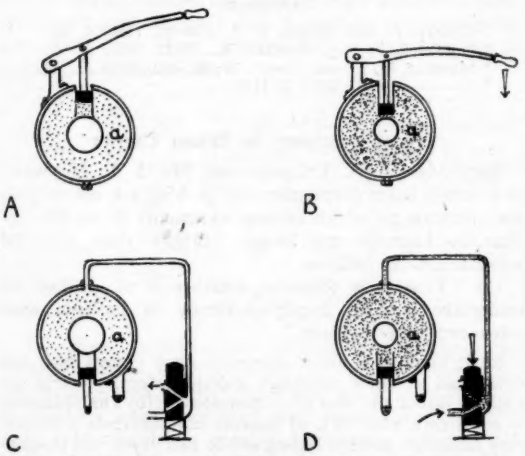
"Automatic controls are available which reduce the duties of the nurse to opening and shutting the autoclave door, loading and unloading the autoclave, and pressing a switch to start the process of sterilization, which then follows automatically and in sequence so that procedures, times and temperatures are maintained without risk of human error. There are obvious advantages in this, but the equipment is *most expensive*, and, in general, it is considered that the additional cost is unwarranted."

One wonders what a progressive manufacturer would do if given the opportunity of installing apparatus which eliminated human error and saved manpower. Of course, nurse-labour is cheap although not plentiful. If a human error occurs the risk is only to a human being. One wonders if this urge for economy applies also to other departments, such as the offices where mechanical accounting machines are installed. No doubt these facilitate the complicated calculation which gives the comparative cost of operations between one hospital and another. Perhaps one may hope that a more enlightened view will be adopted so that further expensive time is saved and foolproof equipment such as ultrasonic instrument-cleaners will be made available.—I am, etc.,

Plymouth. Edric Wilson.

Sir,—With reference to Dr. V. D. Allison's article, "Hospital Central Sterile Supply Departments" (September 10, p. 772), mention is made in his recommendations that research should be undertaken for the development of a foot- or power-operated capping machine. It may be of general interest to know that at the Odstock Branch of the Salisbury General Hospital we have modified an existing capsuling machine to a semi-automatic process.

The modification is as follows: A and B in the diagram show the normal mechanism of a hand-capsuling machine. When the hand lever is depressed the pressure in chamber (*a*) (which contains oil or water) is increased, causing the rubber cuff to bulge inwards around the capsule on the glass needle tube or aluminium



A and B show a typical type of hydraulic capsuling machine. In B the lever is depressed, and the water container in chamber (*a*) is compressed and the central rubber cuff contracts. In C the capsuling machine has been turned upside down, the lever removed, and the filling cap connected through a pipe to a compressed-air supply via a two-way poppet or piston valve. In D the valve is depressed, and compressed air constricts the rubber collar.

container. The handle is somewhat awkward and tedious to use and has been discarded. The machine has been turned upside down and clamped to the bench. The filler plug is tapped and connected to a pneumatic system (see C and D). A light touch of the poppet valve with the foot allows air at a predetermined

pressure to enter chamber (*a*) and produces the same result as depressing the handle. Releasing the valve cuts off the pneumatic supply and allows air to escape from the pressure chamber. The whole process takes a fraction of a second, and the pressure exerted on the capsule is constant irrespective of the fatigue on the part of the operator. In practice operators have found the system easy to use and both hands are left free to place the caps on the containers.—We are, etc.,

E. J. O'Mullane.
A. J. Ogg.

Salisbury General Hospital, Wilts.

Emergency Supplies Rooms

Sir,—An Emergency Supplies Room is a room in which is stored, ready for immediate use, all the equipment which could be required by any ward or department for the treatment of any urgent case. Its contents depend on whether there is central sterilizing in the hospital or not, and on whether oxygen and other gases are piped to the wards and theatres or not. If neither is available then the Emergency Supplies Room is a modified central sterilizing issue room and a central supply room for oxygen and other cylinders. Its situation depends on whether or not there is central sterilizing. If this is available the Emergency Supplies Room should be situated adjacent to the central sterilizing issue room. If it is not then the Emergency Supplies Room should be sited centrally within easy reach of the wards and departments. One Emergency Supplies Room is required for every 200/250 beds, but this depends on the hospital layout, on the site of the lifts, and on the type of illness treated in the wards.

The Emergency Supplies Room has certain definite advantages: (1) It is a room to which the staff can go in an emergency and be sure that they can collect all the equipment necessary to cope with that emergency. (2) It is time-saving and eliminates the necessity for inter-ward borrowing. (3) It is an economic measure in that ward and department stocks of items held in the Emergency Supplies Room can be cut to their basic requirements. (4) If there is no central sterilizing it has most of the advantages of a central sterilizing issue room. (5) If there is no piped gas supply it can be used as a central cylinder store. (6) Blood can be kept in a refrigerator in the Emergency Supplies Room for use while awaiting deliveries from the area blood bank.

The Emergency Supplies Room must be staffed day and night. An Emergency Supplies Room as described has been in operation in a Kuwait General Hospital for two years and has been found to be of inestimable value.—I am, etc.,

Kuwait, Arabia. D. W. A. McCreadie.

Resuscitation Apparatus

Sir,—Two, or even one, Mason's gags, which are found on most anaesthetic machines, will serve as very efficient rib-spreaders in those cases of cardiac arrest in which cardiac "massage" is indicated.—I am, etc.,

The Middlesex Hospital, London W.1. G. L. Zeitlin.

Intra-articular Steroids

Sir,—Intra-articular hydrocortisone is a useful palliative agent in arthritis of the knee, but by itself it is only a palliative, and moreover one which carries the risks of a neuropathic type of arthropathy if used too often and of diminishing the resistance of the joint to infection accidentally introduced. And the pitcher can go to the well once too often.

Even the worst arthritic knee is symptomatically improved by restoring its muscular control by quadriceps drill, but in the very painful knee the pain inhibits the quadriceps action. Intra-articular hydrocortisone by reducing inflammation gives the quadriceps a fresh start. Used thus as an adjuvant to physiotherapy, hydrocortisone need only be injected at rare intervals and often not more than once, thus reducing the risks of its administration.—I am, etc.,

Staines. F. Godsalve Ward.

Suppuration in Rheumatoid Arthritis

Sir,—In 1958 Professor J. H. Kellgren and his colleagues[1] reviewed 12 cases of rheumatoid arthritis in which suppurative complications, chiefly a pyogenic arthritis, occurred. Four more examples of this complication were reported in your journal in letter form.[2–5] As this condition is rare, even in rheumatism departments, I would like to report a further case.

A woman of 56 with rheumatoid arthritis had been attending the steroid clinic for four years. Her disease was well suppressed with 10 mg. prednisolone daily, and a recent E.S.R. was 10 mm. Her general practitioner was called in when she developed a fever of 102° F. (38.9° C.). He could find no fresh signs apart from a purulent urine; started treatment with "furadantin" (nitrofurantoin) and increased her prednisolone. The following day she vomited and the antibiotic was changed to "albamycin G.U." (novobiocin). The temperature subsided, but her right shoulder became swollen and painful. Ten days later an effusion developed in the right knee, with a temperature of 102° F. and further vomiting. After another rigor three days later she was admitted to hospital.

On examination she was afebrile, but looked ill, with a toxic flush and a tachycardia. The right shoulder was swollen and acutely painful, with oedema spreading to the pectoralis muscle. There was a moderate effusion into the right knee, which was tender and held in flexion. Apart from oedema of the shoulder the appearances of the joints resembled an acute exacerbation of her arthritis. The skin of the right arm, however, was erythematous, with a few small papules and pustules. Investigation revealed a haemoglobin of 90%, an E.S.R. of 120 mm., and white cell count of 10,000 per c.mm., with no shift to the left. Cultures of the blood and urine were sterile. An *x*-ray of the knee and shoulder showed no change from previous pictures, apart from some increase in space between the acromium and humeral head. One day after admission she had a further bout of sweating, though the temperature did not exceed 99.6° F. (37.6° C.). The right shoulder was repeatedly aspirated with negative result, but 40 ml. of thick yellow pus was removed from the right knee. Penicillin was injected into both joints and oral tetracycline started. This was changed to intramuscular penicillin when culture grew a penicillin-sensitive *Staphylococcus aureus*. Her condition rapidly improved, but four days later the right elbow developed an effusion with redness and became acutely painful. A few ml. of similar pus was aspirated and penicillin injected. Her haemoglobin fell to 68% and a small blood transfusion was given, but henceforward her recovery was uninterrupted and complete.

It is interesting that her illness started with a fever and urinary infection, with no acute signs in the joints. It is possible, but unlikely, that the urinary infection initiated the staphylococcal pyaemia, but the pustular skin lesions which were seen on admission may well have been responsible. I would like to stress that this condition is very rare, and thus, when it occurs, may be

taken for an ordinary exacerbation of rheumatoid arthritis, especially as both leucocytosis and fever are often suppressed by steroids. A significant fever in this case was not seen in hospital despite the appearance of a fresh joint lesion.—I am, etc.,

Rheumatism Department, West London Hospital, London W.6. M. V. WELLS.

REFERENCES

1 Kellgren, J. H., Ball, J., Fairbrother, R. W., and Barnes, K. L., *Brit. med. J.*, 1958, **1**, 1193.
2 Allum, T. G. L., ibid., 1958, **1**, 1479.
3 Atkins, P., and Brand, J. J., ibid., 1958, **1**, 1479.
4 Thompson, M., ibid., 1958, **2**, 451.
5 Knox, J. D. E., ibid., 1958, **2**, 639.

Rheumatoid Neuropathy

SIR,—In your excellent annotation concerning rheumatoid neuropathy (May 28, p. 1628) you state that the view "is no longer tenable" that the neuritis of diabetes mellitus is vascular in origin. I would be most interested in the basis for your statement. I had thought that the hypothesis of a vascular aetiology for diabetic neuropathy was not yet extinct, especially in view of Fagerberg's painstaking histological study[1] demonstrating significant calibre reduction in intraneural vessels of diabetics and a higher frequency of periodic-acid-Schiff staining in these vessels of diabetics as compared with those of controls.—I am, etc.,

Veterans Administration Hospital, Ann Arbor, Michigan. ARMIN E. GOOD.

REFERENCE

1 Fagerberg, S. E., *Acta med. scand.*, 1959, **164**, Suppl. 345, 1.

*** Perhaps "no longer tenable" was a little provocative. Whilst it is true that Fagerberg (and others) have demonstrated arterial lesions in association with diabetic neuropathy it does not follow that these are necessarily the cause. As Garland points out[1] there is a good deal to be said against this possibility, the fact that it is often absent in patients with marked arterial involvement and that the symptoms may be totally reversible by diabetic control alone, for example. Moreover, Pickering[2] draws attention to the fact that the pattern of nerve involvement is unlike that of ischaemia, and, as we pointed out, there are clear differences in the neuropathy of polyarteritis nodosa in which arterial involvement is responsible. Finally the phenomenon of diabetic amyotrophy has to be explained, in which there is no evidence of an arterial aetiology and in which the cause is most probably metabolic.—ED., *B.M.J.*

REFERENCES

1 Garland, H., *Proc. roy. Soc. Med.*, 1960, **53**, 137.
2 Pickering, G., ibid., 1960, **53**, 142.

School Phobia

SIR,—Your leading article (September 17, p. 848) gives an admirable description of the personalities of children who suffer from a school phobia and of their parents, but we would like to make one or two comments.

Although it is true that these children are tied to their mothers and the origin of the symptom does not lie in the school but in the ambivalent relationship at home, it is not strictly correct to say that school phobia is simply a form of "separation anxiety." If this were so it would be difficult to understand why some of these children accept removal from home—for example, admission to hospital or placement in a school for maladjusted children. Most workers, ourselves included, did not state clearly enough that the danger situation and conflict are removed from home, where they originated, and transferred to school where the anxiety is rationalized and becomes attached to playmates, teachers, achievement tests, etc.[1] In all phobias this important mechanism of "displacement" can be observed (see Freud's classical analysis of "Little Hans," who suffered from a fear of horses).

Whilst it is also our experience that some children who refuse to go to school can be got back quickly by the paediatrician or alert general practitioner, we must never forget that the cure of a symptom, useful though it may be, is not identical with the cure of the underlying neurosis, which in most cases requires expert help. (It is often easy to relieve a cough, but this is not necessarily identical with the cure of the underlying illness.) Child guidance clinics and child psychiatric departments are, it is true, overburdened by the number of cases referred, but it is also true that many children who are eventually referred would not have become so ill had they been referred earlier. The history of patients referred at the point at which their school attendance breaks down usually reveals signs of disturbance preceding the breakdown. We entirely agree[2] with Coolidge *et al.*,[3] who draw attention to a number of patients where the symptom of refusal to go to school is a manifestation of a severe personality disturbance, sometimes even a psychosis. In this case, usually within the adolescent age-group, the withdrawal from school may be part of a schizophrenic withdrawal and isolation.[4]—We are, etc.,

A. MODEL.
E. SHEPHEARD.
Stockport, Cheshire.

REFERENCES

1 Freud, A., *The Psychoanalytic Study of the Child*, 1958, **13**, 102.
2 Model, A., and Shepheard, E., *Med. Offr*, 1958, **100**, 39.
3 Coolidge, J. C., Hahn, P. B., and Beck, A. L., *Amer. J. Orthopsychiat.*, 1957, **27**, 296.
4 —— Willer, M. L., Tessman, E., and Waldfogel, S., ibid., 1960, **30**, 599.

SIR,—Thank you for raising the important issue of school phobia in your leading article (September 17, p. 848). I fear, however, that this does not seem to fulfil the promise of its title, and deals with the problem in a most superficial way. I hope that the child psychiatrists will deal with that. I must, however, protest against your views on the role of school medical officer. In stating that "child-guidance clinics tend to be so cluttered up with simple cases referred by school medical officers, which would have been perfectly well dealt with by a paediatrician, that they have a long waiting-list, and may be unable to deal promptly with really urgent cases such as children with school phobia," the author is clearly not aware of the work, interests, and responsibilities of the school medical officer. May I therefore be allowed to outline the somewhat ill-defined position of school medical officer *vis-à-vis* the paediatrician?

The latter sees the child in hospital only, while the school medical officer sees him at school, and, if there is no occasion to see him at home, finds out all about his background from the health visitor, with whom he works in close co-operation. The school medical officer knows the child's teachers (they occasionally will cause him to stammer too), can influence them, and co-ordinate the treatment through more direct and personal contacts.

One of the many responsibilities of the maternity and child welfare and school medical officer is to educate the parent towards the best parent–child relationship. This he does during various phases of his work, starting

in fact before the child is born—i.e., in the antenatal clinic. The prospective mother's fears and worries are then discussed, and she is helped to develop a more mature attitude towards her motherhood. She is seen again in the infant-welfare clinic about three weeks after confinement, often anxious and very depressed. Attention at this time is centred on the mother rather than the child, because we know that it is she who will provide the right climate for the child's development. Later on, following the child in the infant welfare and toddlers' clinic, we remind the parents of the child's need to be encouraged in his move towards independence, which in turn will help him in developing personality and character, and thus strengthen the bond of affection with his family. Such reassuring advice and influence can work only as a preventive measure, and will not cure an accomplished case of school refusal. During the child's school-life the school medical officer watches his growth and development, advising, encouraging, helping to resolve difficulties often occasioned by the child's puberty as well as by his mother's menopause.

Looking through cases referred to child guidance clinics during the last eighteen months, I have noted the following: (1) Truancy with court action pending, boy aged 7. (2) Aggressive and violent behaviour at school, with court action pending, boy aged 6. (3) Agoraphobia with persistent rocking and other obsessional traits, girl aged 8. (4) Severe stammer in a child with excellent verbal performance, boy aged 6. (5) Encopresis and running away from home, boy aged 8. (6) Persistent stealing at school with poor educational attainment in a child of high intelligence, girl aged 9. (7) General depression and withdrawal in a seemingly insensitive girl of 8, much neglected at home, and few others equally urgent. I doubt whether any of these cases could be effectively treated by a paediatrician. I feel he would strongly resent my "cluttering up" his department.—I am, etc.,

London S.W.19. ANNA L. FRENKIEL.

Lumps in the Breast

SIR,—The letter (September 17, p. 857) in which Mr. Brian McN. Truscott and Dr. David G. Bratherton complain of the neglect of lumps in the breast by doctors—presumably general practitioners—is founded on information given by "an alarming number" of nurses on the word of an unspecified number of patients—information apparently accepted at its face value by the two writers. Now the sort of patient who, in the writers' words, needs "great efforts" on the part of a nurse to be persuaded to report a possible growth in the breast to a doctor is almost certainly stupid and unreliable, and the same, with possibly other attributes, would apply to the sort of nurse who would produce such unlikely tales of false reassurance by doctors to possible sufferers from cancer of the breast. It is surely, to put the matter on the lowest basis of self-interest, quite incredible that any doctor who has to face the family of a patient for the rest of his working life, and who depends on the good will of his neighbouring public for his living, will reassure and send away a patient with a possible growth in the breast. I cannot believe that many of us are stupid enough for that. One may also ask what proportion of patients with a lump in the breast will be seen by a nurse in the first instance. Very small indeed. The nurse does, as the writers say, come into close contact with her patients, but these are the acutely ill to whom she has been called by the doctor and they are not those with early growths in the breast.

It is to the credit of the writers that they have produced their comments in the *Journal* and not, like some members of the medical establishment, in the lay press or on television. As an example, in the *Sunday Times* of August 28 a "consultant physician" wrote as follows: "It is matter for regret that these improvements in hospital services have not been matched by comparable improvements in general-practitioner services." In this rather priggish and smugly complacent statement he makes an assumption the truth of which is very much open to question. Numerous other similar cases have occurred in the medical and lay press and on television—on the latter mostly by innuendo.

General practitioners are easy targets for critical attacks. They do not defend themselves and they do not counter-attack. Possibly their glass houses are more easily destructible than those of their critics. It is likely that they contain a slightly higher proportion of indifferent workers than the consultant body, for they escape earlier from the rigorous moulding into orthodox respectability that is the lot of the budding consultant to-day. But this does not excuse the vague general criticism, unbacked by chapter and verse, so frequently made of general practitioners by a small minority of eminent medical men. If a member of one section of the profession feels it is his duty to criticize a member of another he should do it face to face or by letter, keeping in mind the laws of slander and libel. This might ruffle some feathers, but at least the motives involved would be above suspicion and the possible exchange of a few home truths would benefit both the critic and his target.

Another important point is that public criticism of doctor by doctor is always eagerly seized on by political popularity seekers and by that watchdog of the public interest, the British press. As a result the standing of the profession in the community is damaged, particularly among those in occupations ancillary to medicine, though fortunately our patients seem to treat general criticisms with the contempt they deserve.

We are all prone to error, whether pundit or general practitioner, and medicine is still such an inexact science, and still contains so many different schools of thought, that it affords many opportunities for those who wish to make their colleagues look foolish. Let us all, therefore, in the best interests of the profession, abjure the role of the Pharisee and let us take the beams out of our own eyes before bothering about the motes in the eyes of others.—I am, etc.,

Bath. W. B. S. CRAWFORD.

Sewage in the Sea

SIR,—Being the mover of the "flabbergasted" motion, I must reply to Dr. K. J. Grant's letter (September 3, p. 734). We are disturbed by the conclusions drawn from the Medical Research Council's report because they are positive conclusions drawn from negative facts—the polluted beach has not been found to be harmful, therefore it is for all time harmless, or an unexploded bomb has not yet gone off, therefore it will not go off.

The one positive piece of evidence, somewhat reluctantly admitted in the report, is that four cases of paratyphoid fever have been contracted from bathing from polluted beaches, but to console us we are informed that, as enteric fever is a contracting disease, in the future "the *risks* will be smaller." (The italics are mine.) I pointed out at Torquay that there is no proof statistically or scientifically that at some future time with increasing pollution and with an increasing population of bathers the risks could not be greater.

Our next point, that the report would engender an attitude of complacency on the part of those responsible for the disposal of sewage into the sea, cannot be disputed seriously. Of course it will, and it is not the local authorities that are entirely to blame. The cost to most single authorities would be prohibitive, and it must be planned at a national level. It is clear from the recent debate in Parliament that the Government is only too ready to seek refuge from its responsibilities in the findings of the Medical Research Council's report.

Our third point, that "cleanliness is public health," stresses again that the practice of medicine is an art as well as a science. When we think of the public health nowadays we more and more think of the total human being in a total environment, and this is not just a matter of micro-organisms. It was in this context that I said "the B.M.A. is regarded as the watch-dog of the nation's health." There is an "audible" voice which is properly no concern of the Medical Research Council committee, but to which the British Medical Association must pay some heed. The Medical Research Council report must be recognized as an important piece of research, but on no account can it be regarded as the final word, nor the only word on this problem.—I am, etc.,

Southampton. W. H. N. Angus.

Wounds of the Eyelids

Sir,—Mr. A. N. Guthkelch's most interesting article (September 17, p. 842) points a cautionary tale. It reminded me of another vivid example in which a seemingly trivial wound of the eyelid concealed a serious and extremely unusual intracranial lesion. The case was treated by Mr. Eric Turner at the neurosurgical department, Birmingham.

A 30-year-old woman was involved in a minor road accident while a passenger in a car, and struck her forehead against the door, sustaining a laceration three-quarters of an inch (2 cm.) in length of the upper eyelid. This was thoroughly probed and sutured. She had been momentarily concussed and had a headache with some confusion for several hours. Thereafter she remained entirely well and symptom-free except for drooping of the eyelid which persisted. *X*-ray of the skull, however, showed fracture of the left orbital roof with elevation of a small spicule of bone, and for this reason she was persuaded, with some difficulty, to undergo operation for dural repair to the orbital roof.

Accordingly, 15 days after the accident, left frontal craniotomy was performed and the orbital roof exposed. The spicule of bone was removed, and beneath it we were surprised to find a dense, yellow mass lodged firmly in the bone, penetrating the dura, and lying in apposition with the frontal pole of the brain. This turned out to be an almost intact plastic knob, half an inch by three-quarters of an inch (1.3 × 2 cm.) in diameter, and was easily removed.

She made an uneventful recovery, and subsequent investigation was able to confirm that such a knob was missing from the window lever of the car door against which she had struck her head.—I am, etc.,

Department of Neurology, The Radcliffe Infirmary, Oxford. W. A. Lishman.

Eye-pads for Corneal Abrasions

Sir,—With regard to Mr. O. Gayer Morgan's remarks (September 17, p. 858) on my article (September 3, p. 713), may I point out that the primary object of the article was to attempt to evaluate the relationship of padding to the rate of healing of corneal wounds of a superficial nature? It is my opinion that the survey has shown that padding was of no value from this point of view. Further, I would like to draw attention to the fact that all the complications occurred in the padded group, including that of "recurrent erosion," and, while the number of complications is small, nevertheless they provide food for thought.

We did think about the pain factor, but in order to simplify the experiment it was decided not to consider this aspect of the matter for the time being. However, if it could be shown that pain was not favourably influenced by padding, then the case for discarding the pad would be unassailable, especially since we are likely to reduce the number of complications, including that of "pad abrasion," a not uncommon sequel to the use of a pad and bandage.—I am, etc.,

London N.W.1. Harold Jackson.

Hypnotic Treatment of Asthma

Sir,—Dr. Griffith Edwards (August 13, p. 492), in describing his experience in treating asthmatic patients with hypnosis, comments on the poor immediate response. Rightly, he mentions that mucosal oedema and bronchial plugging are features of severe asthma, whatever the cause. The resolution of these cannot be expected to be rapid, though emotionally determined muscle-spasm may well be. Dr. Charles Burns (September 10, p. 803) has found that immediate relief may often be obtained by hypnosis. That such relief does not always produce a desirable outcome is shown by the following case.

An electrician aged 64 was first admitted to hospital with asthma on July 24, 1958. For 20 years he had suffered with chest-cold in the spring. In the 18 months before admission he gradually became more short of breath, and for the last year had a productive cough and wheezing. For a month he had been incapacitated. On admission he was rather fat and moderately breathless at rest, and continually wheezy. He had a moderate blood eosinophilia. The sputum was tenacious, mainly mucoid, and contained mixed organisms. He was treated with antispasmodics by mouth and by inhalation, but after initial improvement he gradually became more breathless and wheezy. Broad-spectrum antibiotics did not help, and during the second half of August he needed periodical injections of adrenaline and aminophylline. He did not improve, and early in September he was started on prednisolone. He then improved considerably, relapsed when the dose was reduced, but by mid-October was able to go home, taking 7.5 mg. of prednisolone daily. He later returned to light work.

In December he deteriorated despite an increase in steroid dosage, and was readmitted with severe asthma early in January, 1959. His course was very stormy, and at the beginning of March he was still requiring periodical injections of adrenaline, 25 mg. of prednisolone daily, and chlorpromazine. Tension and anxiety had become more evident during this period in hospital, but rapport between him and the staff was always good. He then improved slowly, and hypnosis was started as an adjunct towards the end of March. Suggestions were made that the wheezing and tightness would gradually clear, that he would feel relaxed, and that he would sleep peacefully. He continued to improve, and was discharged on April 12, but still taking 20 mg. of prednisolone daily. Hypnosis was induced again on two occasions as an out-patient, and the dose of prednisolone was gradually reduced.

He was readmitted on May 7 in fairly severe status asthmaticus. He was cyanosed, had a normal blood pressure and a pulse rate of 125 per minute. Subcutaneous adrenaline was given. He had hardly slept for the previous 36 hours, so relaxation and sleep were induced with

hypnosis. His breathing eased, his colour improved, and he was told to sleep for half an hour. He woke at the appropriate time, seemed better, and rang for his supper. When this was brought shortly afterwards he had collapsed, and he died within five minutes.

In my experience, death after initial improvement in status asthmaticus is not uncommon, and post-mortem examination shows plugging of the small bronchi and the bronchioles by secretion. Consent for post-mortem examination was not obtained in this case, but I believe that such would have been the findings. It could be said that in this case hypnosis acted in the same way as over-sedation, by easing the fight for breath on which survival depended. Observation during the time he was asleep suggested that this was not the whole explanation. —I am, etc.,

Ransom Hospital, Nr. Mansfield, Notts. D. DAVIES.

SIR,—In his interesting paper (August 13, p. 492), Dr. Griffith Edwards describes the effects of hypnosis on the respiratory physiology and the clinical response of patients admitted into hospital with severe asthma. In order to obtain any marked physiological change as a result of hypnosis the patient has to reach a deep hypnotic state, which is unlikely to be achieved unless there has been four to eight hours of initial training. It is unlikely, therefore, that any of Dr. Edwards's patients were in deep hypnosis in four or five sessions of 10 to 45 minutes each.

It would be too much to expect from any treatment, including hypnosis, that a respiratory physiology which has been disordered for many years and irreversible changes in the lungs could be restored to normal. It is possible, however, to produce under hypnosis such psychological changes in a chronic asthmatic that he may be able to lead a fairly active life and to compensate for his respiratory limitations. The criteria of a cure, if this may be so called in an asthmatic, are: the alleviation of the distressing symptoms and the ability to control these by auto-relaxation or suggestion; regular working attendance; to be able to dispense with the use of antispasmodic drugs, inhalants, steroids, except antibiotics or sulpha-drugs for infection. It is rather difficult to assess the real improvement of an asthmatic treated in hospital. The mere fact of being admitted has often a beneficial effect, probably due to altered environment. Patients often give an untrue report about their symptoms when followed-up in hospital. The patient's doctor is more likely to succeed with hypnosis, as he can establish rapport more easily. He can also assess progress more easily. The case-history of a chronic asthmatic, who has been followed up frequently for nearly three years, illustrates the values of hypnotherapy.

Male, storekeeper, aged 23. He had the first attack of asthma when he was aged 3 years. It followed a frightening experience of having been attacked by a large dog. He had had about three to four attacks per month ever since. He was handicapped at school, and became nervous, self-conscious, and developed an inferiority feeling. He had treatment in a general hospital, chest hospital, and psychiatric hospital. He had breathing exercises for over two years, and psychotherapy twice a week for two years. He was assured at his last attendance that his asthma was finished, but still he was unable to continue in his jobs because of asthma. He was very dyspnoeic and walking with difficulty.

The first hypnotic session was on October 21, 1957, and these continued for three months, once a week. The intervals between the sessions were then lengthened. He was abreacted and given an insight of his problems. He was a good hypnotic subject. He improved as treatment progressed. He now walks to and from work for a distance of two miles each way without any dyspnoea. On only two occasions in three years has he had to have an antispasmodic, otherwise he takes no drugs, except for one gramme of sulphadimidine daily as a prophylactic against infection. He has only been absent from work for two days in three years, and he is able to go out in all sorts of weather, including fog, which he could never do before. He is able to relax if he gets some bronchospasm, which then disappears. The fact of his being able to do this removed the anxiety about his illness. The sensitivity to feathers which he had had since childhood disappeared as a result of hypnotic suggestion, and since June, 1958, he has been able to use feather pillows without getting any bronchospasm. The only physiological tests performed were the peak expiratory flow-rate, and these improved from 140 to 280 litres per minute.

It is evident from this case that treatment must have achieved something more than just an unawareness of the disability. Simple hypnotic suggestions and symptom-removal, by themselves, will have no lasting therapeutic effect in a chronic asthmatic, and one must be prepared for a longer course of treatment than four or five sessions, if success is to be achieved. The practical aim of any treatment is the relief of symptoms and ability to work, irrespective of any theoretical considerations, and this has been achieved in this case. Another important point in the treatment of asthmatics with hypnosis is the saving of the drug bill, which can be very considerable if steroids are used.—I am, etc.,

London S.E.25. A. FRY.

Polio and Injections

SIR,—It is frequently assumed that when an individual who has had injections shows signs of poliomyelitis the location and extent of the paralysis is governed by the site and frequency of the injections—see, for example, the letter by Dr. W. P. Sweetnam (August 20, p. 603). Why not syringe-transmitted poliomyelitis?—I am, etc.,

Bordon, Hants. JOHN MACKAY-DICK.

Doctors' Letters

SIR,—Of course the medical staff of hospitals should write letters to the patients' own doctors whether or not these patients come to hospital with letters. It is no doubt true that many patients do drop into a casualty department without having gone to their own doctor, but on the whole, certainly in my experience, medical attention has been required and it is most important, and certainly only courteous, to inform the patient's doctor of one's treatment.

There is one plea, however, which I would like to make. I see many patients in the out-patient department, nearly all with a letter from the general practitioner, but only rarely is any relevant therapy that the patients are having or have had ever mentioned. I make it a point to ask the patients if they have had any medicine or tablets, and, if the answer is yes, there comes the laborious and often sterile attempt at identifying the drug or drugs. Occasionally the patients bring tablets along, but even this can present difficulties as some different tablets look the same.

Where therapy matters most is with an emergency admission. To quote but one example where a doctor failed to inform the hospital staff of a patient's therapy

was in an epileptic admitted for a different disease and too ill to inform his attendants that he was an epileptic. I think I have made my point. I hasten to add that this patient fortunately did not have a fit.—I am, etc.,

Chase Farm Hospital, Enfield, Middlesex. S. E. Josse.

Non-smoking Wards

Sir,—The petition signed by registered medical practitioners throughout the country (see *Journal*, April 23, p. 1276) has now been presented to the Minister of Health, asking him to provide separate accommodation in all hospitals for patients who cannot tolerate any form of tobacco smoke and who wish to have their clinical investigations and treatment in wards free from tobacco air pollution.

Practitioners who omitted to sign, and any members of the general public who desire this reform, which is long overdue, are asked to write personally to the Minister of Health, Savile Row, London W.1.—I am, etc.,

Leeds 8. David A. Herd.

R.M.B.F.

Sir,—I am sure that a great many more busy people of good intentions would contribute to the Royal Medical Benevolent Fund (September 17, p. 853) if they realized how simple is a deed of covenant, and how satisfactory it is to feel that a sum over and above the actual amount given is thereby transferred from the Commissioners of Inland Revenue to the R.M.B.F.

A postcard to the secretary of the R.M.B.F., the completion of the form received, and that is all the effort involved. A deed of covenant could be made for even the small sum of one guinea annually (to be continued for seven years but cancelled by earlier death of the donor), and if a sufficient number of B.M.A. members would do this the Fund would be in a much more stable position. A deed of covenant, although perfectly legal, gives one such a delightful impression of cheating the income tax.—I am, etc.,

Hove. Vera E. Claxton.

R.C.O.G. Tumour Registry

Sir,—In your issue of September 24 (p. 942) there is a letter from Dr. K. D. Bagshawe which ends with the plea that there should be set up in this country a registry of trophoblastic tumours, on the lines of the Mathieu Registry established in the U.S.A. in 1947.

In January of this year the Royal College of Obstetricians and Gynaecologists, with the support of the Pathological Society of Great Britain and Ireland and the Association of Clinical Pathologists, decided to extend the scope of its tumour registry. The fellows and members of the three bodies have been asked, and clinicians and pathologists invited, to submit to the registry any of the following material: clinical data (on forms to be supplied); pathological tissue; paraffin blocks; histological sections; the address to which all communications should be sent being the Registrars, Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London N.W.1.—I am, etc.,

London N.W. Ian Jackson,
Hon. Secretary,
Royal College of Obstetricians and Gynaecologists.

Obituary

A. M. KENNEDY, M.D., F.R.C.P.

Professor A. M. Kennedy, emeritus professor of medicine, Welsh National School of Medicine, and honorary consulting physician to the United Cardiff Hospitals, died suddenly on September 24 at St. Winifrede's Hospital, Cardiff. He was 75 years of age.

Alexander Mills Kennedy was born on March 3, 1885, the son of the late Alexander Kennedy, O.B.E., J.P., F.S.A., of Bothwell, Lanarkshire. Educated at Allan Glen's School and at the University of Glasgow, he graduated M.B., Ch.B. in 1908 and proceeded M.D. with honours in 1912. He took the M.R.C.P. of London in 1927 and was elected to the Fellowship in 1933. After qualification he held a number of posts in Glasgow, including those of resident physician and senior assistant pathologist at the Glasgow Royal Infirmary, and senior assistant to the professor of pathology in the University of Glasgow. During the first world war he served first with the British Red Cross, and then from 1915 as a pathologist in the R.A.M.C., being mentioned in dispatches. On his return to Glasgow he became senior assistant to the professor of medicine in the University, assistant physician at the Royal Infirmary, and director of the research department at the Royal Maternity and Women's Hospital, Glasgow. In 1921 he was appointed the first professor of medicine in the University of Wales, working in the Faculty of Medicine at the Cardiff College. As he often used to say, he was caught young.

The appointment of a full-time professor at Cardiff was one of the earliest of such full-time appointments, and was far from popular among some of the members of the staff of the Cardiff Royal Infirmary at that time. When he arrived in Cardiff Professor Kennedy had a bare dusty room and no furniture. With the help of a porter he collected a table and a few chairs which were brought to the Cardiff Royal Infirmary as his initial equipment. However, by 1925 the University of Wales obtained a grant from the Rockefeller Foundation with which they built a four-story laboratory for his use at the Cardiff Royal Infirmary, a laboratory which he designed and planned. He was soon made dean of the Faculty of Medicine and later played an active part in the establishment of the Welsh National School of Medicine, which was finally constituted in 1931.

Many will still remember the bitter controversies of those years with the closing down for 12 months of medical teaching owing to the withdrawal of the beds of certain members of the consultant staff, but few now realize the difficulties with which Professor Kennedy had to contend. He carried out a task which would have crushed or embittered a lesser man, but he stood up to local prejudices unflinchingly, sacrificing nothing which he considered important, and eventually guided the Medical Faculty, and later the Welsh National School of Medicine, into calmer and more tranquil times. At all times he held firmly to his high standards of what was required for the proper training in clinical medicine and to the standards he considered necessary to obtain the M.B. of the University of Wales. The Welsh National School of Medicine must always be grateful to him for his help and guidance in those early years, and for the sound basis on which he started and for many years upheld the standard of training in medicine at Cardiff. A

sincere man himself, he had no use for insincerity in others. Next to his devotion to his university was his devotion to his students, and for them nothing was too much trouble. He maintained throughout an active and lively interest in each individual. He was always interested in young people, and for many years his was a familiar and energetic figure at the medical freshers' dance, an art in which he was most proficient in his early days and reflected his obvious enjoyment of life. On the wards and in his unit he was a kindly but rigid disciplinarian. Before going on his wards students were fully instructed on how they were to conduct themselves. Not infrequently, when he felt things were getting lax, he would hold an inspection of students outside the ward. He would line them up and inspect their personal appearances, especially their hands. Those who did not pass his scrutiny were sent away to wash their hands and scrub away nicotine stains. Woe betide the student who, having been warned, turned up in a grubby white coat. But if his manner appeared gruff there was a warmth and kindliness and a sense of fun behind it which endeared him to his students. "Jock," as he was known to many generations of students, was at all times regarded with affection. One of his most treasured possessions was a gold watch given him by the students on his retirement.

A round with the professor was an event, an event to which all looked forward—his assistants, his students, and not least his patients. He was a master of the art of history taking and of eliciting physical signs. Time and again he showed how an apparently difficult case could be solved by a careful, painstaking history and by an equally careful examination. It was this careful attention to the history and physical signs which he instilled so thoroughly into his students and for which so many have cause to be grateful to him. Many treasure the memory of "Jock's" rounds, with his pleximeter and his wooden monaural stethoscope.

His interests in medicine were wide, and his original contributions to the medical journals frequent, covering various aspects of haematology, neurology, and cardiology. He wrote three books, *Cerebro-spinal Fever: The Etiology, Symptomatology, Diagnosis and Treatment of Epidemic Cerebro-spinal Meningitis* (with C. Worster-Drought); *Parasitology for Medical Students*; and *Medical Case-taking*. He was a member of the Association of Physicians and one of the earliest members of the Cardiac Club. Having been vice-president of the Section of Medicine at the Annual Meeting of the B.M.A. in 1926, he was president of the section at the Cardiff meeting in 1953. His interests extended beyond medicine, and he had an excellent collection of paintings and etchings which he delighted to show and explain to his friends.

The Welsh National School of Medicine and the many generations of students whom he taught owe much to Professor Kennedy and will always cherish his memory. To his sister goes our deepest sympathy.—D. A. W.

L. C. R. writes: A. M. Kennedy came to Cardiff at a difficult time in the history of its medical school. He was the first professor of medicine in the newly created clinical school with his beds at the Royal Infirmary, which was still in a stage when several members of its staff were in general practice. He had to do pioneering work, not without opposition, in establishing his teaching unit, and he was unable to forget the resistance which he met with from some quarters; but he was a first-class clinician and an excellent teacher who propounded sound principles. He was also a disciplinarian, insisting on tidiness and proper deportment on the part of his students. They on their part appreciated his care for them, and when in September, 1950, he retired after occupying his chair for nearly 30 years, they did an unprecedented thing in their club by entertaining him and presenting him with a gold watch as a token of the esteem in which they held him.

His influence in the school of medicine was good; he had no use for humbug, and self-advertising of any kind was anathema to him. He was absolutely honest and forthright in his opinions and there will be many who will miss his pawky humour and often deliberately provocative statements, made, however, without malice and with a merry twinkle in his blue eyes. Though small in stature his presence was felt and his opinion, expressed in a few words, was weighty and could not be disregarded. Many in practice or on the staff of hospitals have much for which to thank "Jock" Kennedy and are the better for having been associated with him.

N. J. writes: Professor "Jock" Kennedy made an immediate impact on each of us from our first day in hospital, and the basic knowledge of clinical medicine which we learnt from him bears witness to the continuing success of his teaching. His kindness, consideration, and tact were often concealed by an astringent wit which enlivened his rounds and served to cloak his gentleness and reserve. In all his dealings with patients, staff, and students he combined common sense and good judgment with an integrity which inspired absolute trust. His unfailing courtesy created an atmosphere of calm orderliness which helped to make the medical unit a training ground for character as well as mind. Each morning before we entered his wards he talked to us of many things; we learned the value of punctuality, good grooming, and how to approach each patient with a silent walk, a quiet voice, and gentle hands.

To him medicine was an art, difficult to acquire but infinitely rewarding. While insisting on accuracy of perception and the writing of a lucid history, he always emphasized the importance of treating every patient as a whole person. His approach to medicine was coloured and enriched by his wide knowledge of literature, poetry, and the arts. In his retirement he derived much satisfaction from painting, in water colours, scenes from the countryside and west coast of Scotland.

Until the end of his life he delighted in hearing news of his old students, and gave them a warm welcome whenever they visited him. Many who specialized in different fields owe much of their success to his help and encouragement. His advice, compounded of a clear vision and wide perspective, was couched in terse epigrams which illuminated and clarified each problem.

He never tired of telling us that his heart was in Scotland, "the birthplace of valour, the country of worth," but for half a lifetime he gave of himself to Wales and her sons. When we remember the Professor, we can say with Burns that:

> "The rank is but the guinea's stamp,
> The man's the gowd for a' that."

HENRY ROBINSON, M.D.

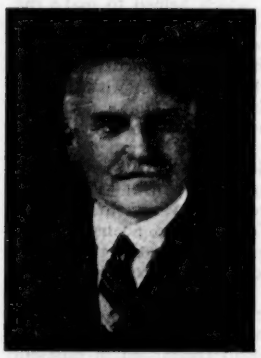
Dr. Henry Robinson, who was formerly in practice in Kensington and was consulting anaesthetist to the Royal Cancer Hospital, died at Tunbridge Wells on September 30, aged 83. For many years he applied his great talents in the service of a number of medical organizations and charities, including the Medical Defence Union and Epsom College, of both of which he was honorary treasurer, of the Medical Insurance Agency, of which he was honorary secretary, of the British Medical Association, and of the Royal Medical Benevolent Fund.

Henry Robinson was born in Kensington on May 29, 1877, the eldest son of Sir Richard and Lady Robinson. With few breaks, he spent the whole of his career in the royal borough until his retirement to Tunbridge Wells. He won scholarships both to St. Paul's School and Trinity College, Cambridge, where he took first-class honours in the Natural Sciences Tripos in 1899. Then he interrupted his student career to enlist as a private and fight in the South African war, serving with the university contingent to the Volunteer Company of the 1st Battalion of the Suffolk Regiment. Returning home, he completed his training in medicine at St. George's Hospital, London, and graduated M.B., B.Chir. in 1903. Five years later he proceeded to the M.D. After house appointments at St. George's, at Great Ormond Street, and at the Royal Cancer Hospital, he settled in practice in Kensington in 1907,

remaining there for more than thirty years, with the exception of his service in the first world war, when he was captain in the R.A.M.C., serving from the outbreak and being the holder of the Mons Star.

When he went into practice specialization was in its infancy, and, as many men did, Robinson combined anaesthetic work with general practice. He held posts as anaesthetist at the Royal Cancer and Samaritan Hospitals and wrote a number of articles on anaesthetics in various journals and textbooks, including Thorpe's *Dictionary of Applied Chemistry*. When Sir F. W. Hewitt was contemplating the fourth edition of his *Anaesthetics and their Administration* in 1912 he secured the co-operation of Dr Robinson, who himself edited the fifth edition in 1922.

Almost as a result of family tradition Dr. Robinson devoted much of his time to local government. His father was the leader of the Municipal Reform Party when it won its first victory in the London County Council election in 1907, and was chairman of the Council in the following year. Henry Robinson himself was a member of the London County Council for six years, and served on the Hospitals Management and the Mental Hospitals Committees at a time when the Council carried a heavy weight of responsibility for hospital improvements. He was Mayor of Kensington in 1928–30, and was a councillor and then an alderman of the borough for many years. He was also a Justice of the Peace and a Deputy Lieutenant of the County of London, and on the coming of the National Health Service he became a member of the London Executive Council.



Dr. Robinson's service to the British Medical Association included his two-year chairmanship of the Kensington Division. For several years he was a member of the Central Council and of a number of committees, including the Finance Committee and Charities Committee. The Association greatly profited from his service as chairman of the Building Committee in 1937–9, at a time when the Tavistock Square property was rapidly developing. He was also at one time a member of the old Board of Directors of the *British Medical Journal* and of the Journal Committee. A frequent contributor to the obituary columns of the *B.M.J.*, he was a mine of information about old St. George's men. He was a representative at several Annual Meetings of the B.M.A., and was a vice-president of the Section of Medical Sociology at Melbourne in 1935.

In 1916 he was elected to the council of the Medical Defence Union, which he served for many years. He was elected honorary treasurer in 1928, and his financial acumen was of inestimable value to the Union. At Epsom College he worked tirelessly for the Foundation, serving in many offices. His financial talents found further expression in his honorary secretaryship of the Medical Insurance Agency, a post he took over in 1938. This was a turning point in the affairs of the Agency, which then entered upon a period of usefulness and success such as it had never previously approached. He had long been a member of the management committee of the Royal Medical Benevolent Fund, and in 1955 he was appointed chairman of its Case Committee.

A man of so many public and professional activities could not have much time for other pursuits, but he was a keen Territorial during the inter-war period, and at the outbreak of the war in 1939 he applied to re-enter the R.A.M.C., but was rejected on account of age. He had by that time retired from general practice but took psychiatric posts in mental hospitals until the end of the war.

Henry Robinson held strong views on many subjects. One of his favourite themes was that the honorary treasurer of a medical organization should be a respected member of the profession and of obvious integrity, but he should also have good knowledge of business matters, finance, and investments. On several occasions it is understood that he declined nomination for election to the presidency of the Medical Defence Union because he felt that he was of more use to the Union as its honorary treasurer.

In 1956 (at the age of 79) he undertook the task of arbitrating a dispute between two practitioners in Nigeria and flew to Lagos for that purpose. The year before he had attended the Joint Annual Meeting of the British Medical Association and the Canadian Medical Association in Toronto.

In 1911 Dr. Robinson married Margaret, youngest daughter of the late Robert Barnes, M.D., F.R.C.P., F.R.C.S., the famous Victorian obstetrician. He is survived by his widow, two sons, and a daughter. All with whom he worked and all those he helped will wish to extend their sympathy to them.

Mr. R. W. RAVEN writes: To those who were privileged to be closely associated with Henry Robinson in his charitable activities, his passing will seem like the end of an era. Two of his most cherished interests were connected with the Royal Medical Foundation of Epsom College and with the Medical Insurance Agency, whose many bequests to medical charitable funds were guided by him.

His interest in Epsom College was aroused in the early 1920s, when Sir Raymond Crawford asked him to become an honorary local secretary. As always, he applied himself most energetically to any task in which he was interested, and so in these very early days he wrote, by hand, several hundred letters seeking charitable contributions for the College. He met with an immediate disappointment, for not a single donation resulted from those first letters. He resolved to write a final ten letters, and three contributions were then received; this success rekindled his enthusiasm. In future years he collected unaided no less than £10,000 in small donations from all parts of the country for the College funds. This sum stands quite apart from the enormous total of other contributions which he helped to bring to the College and to the Royal Medical Foundation. Henry Robinson was first elected to the Council of Epsom College in December, 1926, and became chairman in 1936, holding that office until 1939. He was the first chairman of the Conjoint Committee of Epsom College from its foundation in 1932, and was again elected to that office in 1939–41. In 1952 he was elected treasurer, which appointment he held until his death. Throughout his career he never once missed a meeting, except through absence abroad, and it is typical of the man that once, when returning from British Columbia after a six months' visit, he arrived back in Liverpool on a day when a meeting of the conjoint committee was to be held. He received the agenda on board ship, studied it in the train, and travelled direct to the meeting, where he proved to be the best-informed member of the committee—all this at the age of 80. His knowledge of the medical charities was unrivalled, and his capacity for clear thinking and for figures was the envy of all who served with him.

As regards another of his great interests, the Medical Insurance Agency, he first came into prominence in 1938, when he accepted an invitation to become the honorary secretary, and he served in that capacity until his retirement from the appointment in 1957. Throughout that period he was greatly interested in its expansion and proved a tower of strength in the difficult war years and those immediately following them. Nothing illustrates better his successful association with the Agency than the extent of the charitable donations made by it under his guidance. In 1937, £4,300 was distributed to the medical charities, and in 1957, the year of his retirement, this annual sum had become £24.850. In total throughout that period medical charities benefited by the sum of £270,000. Perhaps on his retirement

the most touching tribute to his charitable work through the Agency was the foundation in perpetuity of four "Henry Robinson" scholarships of £250 per annum each, to be awarded to chosen entrants to Epsom College. No more fitting mark of appreciation of his great gifts could ever have been made, and it is a matter for much satisfaction that he was able himself to choose the first few scholars to benefit from the "Henry Robinson" scholarships.

Henry Robinson was greatly respected and loved by his colleagues and the staff of these organizations. We shall always remember him with great gratitude, and unite in saying, "Well done, good and faithful, enter thou into the joy of thy Lord."

J. A. GUNN, C.B., O.B.E., M.D., F.R.C.S.(C.), F.A.C.S.

Dr. J. A. Gunn, professor emeritus of surgery, University of Manitoba, and a vice-president of the Canadian Medical Association, died in Deer Lodge Military Hospital, Winnipeg, on August 8. He was 82 years of age.

John Alexander Gunn was educated in his birthplace, Stonewall, and in Winnipeg, where he graduated B.A. Manitoba College and, in 1904, M.D. from Manitoba Medical College. In 1907 he was medical superintendent of the Winnipeg General Hospital and later entered into partnership with Dr. R. J. Blanchard, who was one of Lister's first dressers in Edinburgh. When the war broke out in 1914 both partners went overseas, Dr. Blanchard as O.C. No. 3 Canadian C.C.S., while Gunn was appointed O.C. No. 1 Canadian General Hospital at Étaples. For his services he was twice mentioned in dispatches, and was awarded the O.B.E. in 1918 and C.B. in 1919. In 1920 he married in London Armorel Thomas, who, with two sons, survives him.

He returned to practise surgery in Winnipeg, and was appointed chief surgeon of the Winnipeg General Hospital, and, later, of St. Boniface Hospital. At the University of Manitoba he was professor of surgery, being appointed emeritus professor on his retirement. He had become a Fellow of the American College of Surgeons in 1913, and in 1931 he was elected a Founding Fellow of the Royal College of Physicians and Surgeons of Canada. Another appointment he held was that of chief medical officer of the western region of the Canadian Pacific Railway.

He also found time for community duties. He was president of Manitoba Medical Association, a vice-president of the Canadian Medical Association, for many years a member of the British Medical Association, a founding director of Medical Arts Building, president of the Manitoba Club and of the Canadian Club of Winnipeg. The old Roman virtues were exemplified in him, and he deserved the poet's praise, "Integer vitae."

N. A. NEVILLE, B.M., B.Ch., M.R.C.P.

Dr. N. A. Neville, consultant in chest diseases to the Hertford group of hospitals, died on August 16 at the age of 46.

Norman Alan Neville was born on May 11, 1914. He left Whitgift School with a county major scholarship and an entrance scholarship to Queen's College, Oxford, where he graduated B.A. with first-class honours in physiology. Entering Guy's Hospital in 1936 with a university entrance scholarship, he was later awarded the Beany prize in pathology, the Treasurer's Medal and prize in clinical surgery, and the Butterworth prize. Having graduated B.M., B.Ch. in 1939, he held house appointments at Guy's and then served in the R.N.V.R. from 1942 to 1946. After the war he returned to the Guy's Hospital unit at Pembury. At this time the fascination of chest medicine overcame his earlier surgical ambitions (he had passed the primary F.R.C.S. at Oxford), and he was appointed senior registrar at Broomfield Hospital, where he met and married Ada Yell, daughter of the physician superintendent.

He became M.R.C.P. in 1949 and was appointed medical director of the mass radiography unit at Southampton and consultant chest physician. After a short time there he was appointed chest physician to the Hertford group of hospitals, and physician superintendent at Ware Park Hospital. Although by 1951 the tide of tuberculosis had turned, few then thought the ebb would be so rapid, but plans for the rebuilding of Ware Park as a new regional centre for pulmonary tuberculosis were left high and dry. Though the dream faded, his dedication remained, and under him Ware Park, though outwardly unchanged, was inwardly transformed. Fame never was the spur. He had a physician's outlook and a surgeon's hands, and only those who had been his immediate colleagues knew the professional worth of this big, shy, dependable man. But it was with his patients that he found self-expression easiest, and he was able to reveal to them without shyness the kindness that was so much a part of his character, and many share with his widow and his two small sons, of whom he was so proud, a sense of deep personal loss.

J. D. WHITFIELD, M.B., Ch.B., D.P.H.

Dr. J. D. Whitfield, who was in general practice in North London for over thirty years, died at his home at Hornsey on August 28. He was 68 years of age.

John David Whitfield was born on the tiny island of Kulangsu, Amoy, on March 1, 1892, the son of Scottish-Chinese parents. From early childhood he showed great interest in medicine and administering to the sick. At the suggestion of Dr. Lim Boon Kheng, the first doctor from Amoy to study in Britain, he went to Edinburgh University at the age of 18, graduating M.B., Ch.B. in 1915. Three years later he obtained the Cambridge Diploma of Public Health. Having trained under Sir Robert Philip, he was interested in tuberculosis, and became house-physician at the Brompton Hospital, medical superintendent of Mount Vernon Sanatorium, and, later, district tuberculosis officer under the Cheshire County Council. His keenness and thirst for knowledge in other branches of medicine led him to take a practice in North London, in which he remained from 1927 until his death. During this time he became interested in disorders of the foot and in psychiatric disturbances, but continued to specialize in the diagnosis and treatment of diseases of the chest. He was studious, careful, and thorough in all that he undertook, and had a flair for improvisation. He was never happier than when he could "make something useful out of nothing," an accomplishment which appealed to his sense of humour. For many years he lived a secluded, simple life, but retained his enthusiasm for motor-cars, stamp-collecting, horse-riding, tennis, badminton, golf, and dancing, and was never content until he had mastered each of these pastimes to his satisfaction. Although he had suffered from ill-health for the past few years he was always ready to attend to the ailments of others and to help them in their troubles. He will be greatly missed by his patients, to whom he was not only a doctor but also a beloved friend.

G. SCOTT ROBERTSON, M.B., Ch.B.

Dr. Guy Scott Robertson, formerly medical superintendent and consultant psychiatrist at the Calderstones Hospital, Whalley, near Blackburn, died at his home on August 24. He was 60 years of age.

Guy Scott Robertson was born in Scotland on March 8, 1900, the son of Dr. James Robertson, subsequently medical officer of health of Darwen, Lancashire. Educated at

George Dixon's School, Birmingham, and Glasgow University, he graduated M.B., Ch.B. in 1925. He represented his university at both hockey and Rugby football. Joining the medical staff at Calderstones Hospital, Whalley, in 1925, he spent his whole professional career there. His appointment as medical superintendent dated from 1937 until his retirement a few weeks ago.

Dr. Robertson leaves a widow and a son and a daughter.

Speaking at the funeral service held at Calderstones Hospital, the Rev. H. C. Snape, chaplain to the hospital, said that all would regret that Guy Scott Robertson was denied the years of retirement in his native Scotland, but it was befitting that he should have died in the superintendent's residence and that his funeral rites should be in the hospital chapel. For Calderstones Hospital had absorbed all his interests to the exclusion of almost every other, and the welfare of its 2,000 patients and the fortunes of his colleagues and staff were his whole concern. The three qualities which animated and coloured that concern were his patience and forbearance, his sensitiveness, and his faith. It had been said that his heart led his mind. He yearned for peace and harmony. He preferred the velvet glove to the iron hand, diplomacy to force. That came from patience, a much rarer virtue than was commonly admitted. It also came from his sensitiveness. He made the welfare of the patients his whole concern. But no man could have given his whole heart and life to the work of the hospital without a faith in some overriding purpose for life, although Dr. Scott Robertson's own sensitiveness made him chary of the conventional answers, and, in this age of spiritual confusion, of the traditional presentations. The faith which could not find facile expression was expressed in will and action. "By their fruits ye shall know them."

R. F. D. MacGREGOR, C.I.E., *M.C.*, M.B., Ch.B. M.R.C.P.Ed.

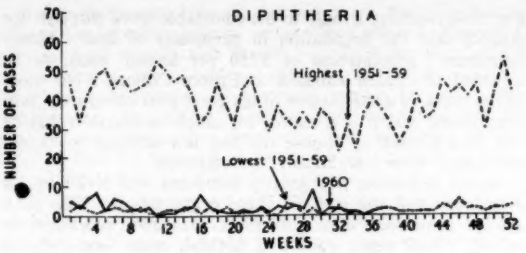
The obituary of Colonel R. F. D. MacGregor was published in the *Journal* of July 30 (p. 395).

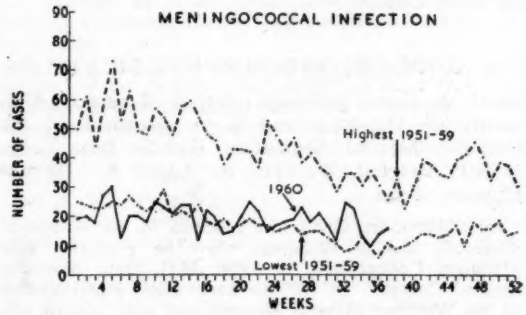
Dr. T. D. RAJOO writes from Secunderabad: It is with the greatest regret that I read in the *B.M.J.* of the death of my dear and respected chief, Colonel R. F. D. MacGregor. He was not only residency surgeon for six years (1933–9) in Hyderabad but he was also the superintendent of K.E.M. Hospital, Secunderabad, where I was the resident medical officer. We in Secunderabad were lucky to have some of the best men in the Indian Medical Service as the head of this hospital, and Colonel MacGregor was of the finest type. Loved and respected by all, rich and poor, he was extremely kind to the poor patients, and sometimes would help them with money from his own pocket. He would go round the hospital every day except on Sundays and see every patient, even though it was a 250-bedded hospital. He was lovingly called "the Padre" by very many poor patients. Britain taught many noble things to India; among them were punctuality, discipline, sincerity in one's work, sympathy, kindness, and courteousness. If men like Colonel MacGregor succeeded in teaching such principles as these they should feel happy.

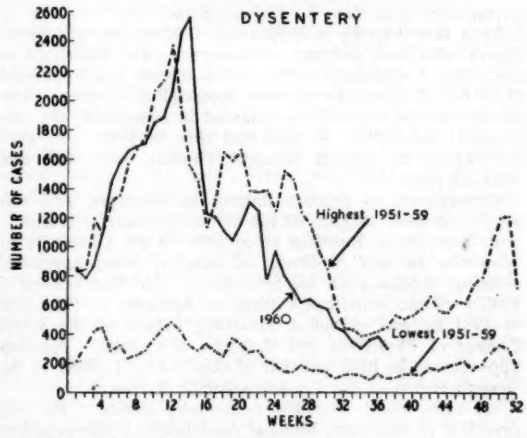
Vital Statistics

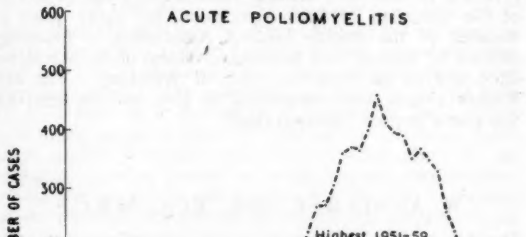
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Road Deaths in July

There were 634 deaths as a result of road accidents in July, 46 more than in the same month last year. The increase of nearly 8% may be partly explained by the fact that July included the Saturday and Sunday of the August Bank Holiday weekend, which last year fell in the month

of August. Pedestrians suffered the most serious increase in fatal casualties: deaths rose by 61 to 206, including 52 children. More motor-scooter riders and passengers were killed than in July last year, but motor-cycle casualties were fewer, probably because motor-cycle traffic was less by an estimated 5%.

The total number of killed and injured during the first seven months of 1960 was 189,672. This was an increase of 5%, while the volume of traffic increased by 9%.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Sept. 17	Week Ending Sept. 24
Measles		
Lancashire	495	**627**
Liverpool C.B.	63	**79**
Dysentery		
Lancashire	45	**56**
Liverpool C.B.	18	**23**
Worsley U.D.	1	**11**
London	46	**86**
Finsbury	2	**14**
Islington	4	**14**
Lewisham	5	**11**
Yorkshire West Riding	56	**74**
Leeds C.B.	22	**23**
York C.B.	5	**15**
Monmouthshire	1	**13**
Ebbw Vale U.D.	1	**13**
Food Poisoning		
Lancashire	28	**55**
Liverpool C.B.	9	**31**
Hampshire	22	**10**
Southampton C.B.	17	**9**

Quarterly Returns for Scotland

In Scotland the birth rate for the second quarter of 1960 was 20.2 per 1,000 population—the largest rate for a second quarter since 1948 and 0.7 above the average of the five preceding second quarters. The infant mortality was 26 and the neonatal mortality rate 18 per 1,000 registered live births, both figures being close to those of the corresponding quarter of 1959. The stillbirth rate was 21 per 1,000 total births. The death rate was 11.4 per 1,000 population, being 0.3 above the rate for the second quarter of 1959 but 0.1 below the five-year average. Deaths attributed to tuberculosis numbered 112 (115) for respiratory and 12 (15) from other forms of tuberculosis (1959 figures in parentheses). Deaths from the principal epidemic diseases numbered 50 and included 42 from influenza, 4 from meningococcal infections, 3 from whooping-cough, and 1 from streptococcal sore throat. Deaths ascribed to cancer numbered 2,738, 25 more than in the second quarter of 1959. Of these deaths 605 (536) were attributed to lung cancer. Deaths from violence numbered 707 (664), of which 235 (236) were due to accidents in the home and 176 (162) to transport accidents.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in August were 94, compared with 140 in the previous month and 51 in August, 1959.

The number of cases of industrial diseases in the United Kingdom reported during August were as follows: lead poisoning 7, mercurial poisoning 1, compressed-air illness 4, anthrax 1, epitheliomatous ulceration 20, chrome ulceration 19, total 52. There were 4 deaths (compressed-air illness 1, epitheliomatous ulceration 3).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 17** (No. 37) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	2	2	2	0		5	3	0	0	
Dysentery	307	46	190	16	3	449	42	227	7	3
Encephalitis, acute	2	0	0	0	1	10	1		1	
Enteric fever:										
Typhoid	2	1	0	0		9	2	1	1	1
Paratyphoid	13	1	0	0		14	0	0	0	4 (B)
Food-poisoning	196	26	10	9		293	29	32	6	
Infective enteritis or diarrhoea under 2 years				21	20				21	63
Measles*	1,087	54	44	4	5	686	29	8	43	63
Meningococcal infection	16	0	25	0		20	3	7	2	
Ophthalmia neonatorum	23	0	4	0		28	6	6	0	
Pneumonia†	123	6	101	3		132	12	103	3	
Poliomyelitis, acute:										
Paralytic	13	7	0	0	7	19	8	0	1	3
Non-paralytic	3	0	0			14	1	3		
Puerperal fever§	127	10	14	2		215	28	15	0	
Scarlet fever	238	15	33	13	22	402	32	84	19	20
Tuberculosis:										
Respiratory	389	41	65	10		366	34	57	9	
Non-respiratory	47	6	8	3		59	3	15	3	
Whooping-cough	1,372	146	122	3	25	718	32	131	7	50

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0		0	0	0	0		1
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	1	0	1	2	3	7	0	0	0	0
Influenza	3	0	0	0	0	1	0	0	0	0
Measles		0	0	0	0		0	0	0	
Meningococcal infection		0	0				0	0		
Pneumonia	389	36	16	15	3	265	18	14	5	3
Poliomyelitis, acute	0	0		0	0	2	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	44	3	3	0	7	61	2	8	1	6
Non-respiratory		1	1	0	1		2	1	0	0
Whooping-cough	1	0	0	0	0	1	0	1	0	0
Deaths 0–1 year	276	24	21	9	8	257	23	19	6	9
Deaths (excluding stillbirths)	8,534	709	536	127	111	7,643	613	463	99	124
LIVE BIRTHS	14,547	1248	931	257	342	13,740	1210	895	261	395
STILLBIRTHS	294	20	22			273	24	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Strontium-90 in Human Diet

The main conclusion in the Agricultural Research Council's report, *Strontium 90 in Human Diet in the United Kingdom 1959*, is that, though more strontium-90 was absorbed in the diet in 1959 than in 1958 because of relatively high levels of contamination early in the year, the estimated level in the diet of the population as a whole represented less than one-twentieth of the maximum permissible level recommended by the Medical Research Council, and decreasing levels may be expected in future. (H.M.S.O., 3s. 6d. net.)

Press and Mr. Bevan's Illness

The Press Council has issued a statement on the allegations made by the Labour Party against the conduct of certain reporters during the late Mr. ANEURIN BEVAN'S stay in the Royal Free Hospital, London.

While appreciating that the hospital's administrative resources were under considerable strain, the Council considers that inadequate arrangements were made to meet the legitimate demand for news. "The press," the statement continues, "has a responsibility to hospitals on such occasions to limit its inquiries as far as possible. This was indicated in the recommended routine procedure at hospitals recommended by a conference of representatives of the medical profession and the press on May 16, 1956, when it was stated that 'satisfactory co-operation between hospitals and the press will depend on the observance of conduct that will promote mutual confidence and good personal relations.'" The Press Council comments on the importance of observing this procedure. Where three specific complaints are concerned, the reporters are exonerated in one, but the Council regrets in the other two cases that some reporters visited an upstairs ward in the hospital to pursue their inquiries. "Undoubtedly they were at fault in doing so." The Labour Party allegation that there had been "unauthorized attempts to gain entry into Mr. Bevan's room" was misleading and not borne out by the evidence.

Honorary Fellowships in Medical History

At the inaugural meeting of the first British Congress on the History of Medicine and Pharmacy held in Apothecaries' Hall, Blackfriars, on September 29, Sir GEOFFREY KEYNES and Professor OWSEI TEMKIN were awarded the Honorary Fellowship of the Faculty of the History of Medicine of the Worshipful Society of Apothecaries of London. The Fellowship, which is an exclusive award to be held by no more than 12 persons at any one time, irrespective of nationality, is bestowed for outstanding services to scholarship in the history of medicine and pharmacy.

Sir Geoffrey Keynes, the first recipient of the new honour, is known for his work on Harvey, Sir Thomas Browne, John Ray, and Robert Hooke, while Professor Temkin, who is director of the Institute of the History of Medicine in Johns Hopkins University, Baltimore, has made many studies of classical and mediaeval medicine, his monograph on *The Falling Sickness* being the most widely known of his works. An article on the Congress is on p. 1083 of the *Journal*.

Medical Defence Union

The Medical Defence Union, the oldest as well as the largest defence organization in the world, celebrated the seventy-fifth anniversary of its foundation in 1885 with a dinner at the Apothecaries' Hall on October 4. Many distinguished guests were entertained, including the Speaker of the House of Commons, Sir HARRY HYLTON-FOSTER, and the presidents of the General Medical and Dental Councils, Sir DAVID CAMPBELL and Sir WILFRED FISH.

The toast to the Medical Defence Union was proposed by Sir HARRY HYLTON-FOSTER, and Dr. S. COCHRANE SHANKS, the President, in his reply, spoke of the work of the Union, explaining not only how it protected doctors and dentists against unfair charges, but also how it helped the public in their just claims. By the end of 1945—after the first 60 years of its existence—the Union had incurred the sum of £290,387 in costs, legal expenses, and damages in protecting or advising its members, but by the end of 1959—only 14 years later—the total amount paid out by the Union on behalf of its members had reached £873,436. Sir RUSSELL BRAIN, Bt., proposed the health of the guests, and Sir DAVID CAMPBELL replied.

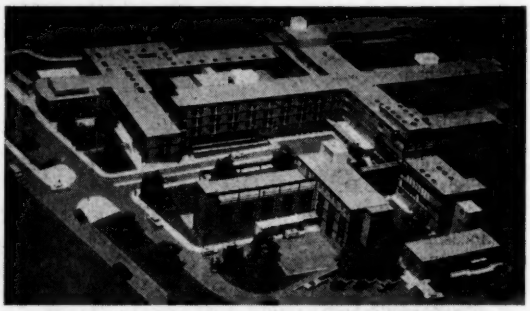
Steroid Reference Collection

The Medical Research Council states that in future all requests for compounds in the Steroid Reference Collection should be addressed to Professor W. KLYNE, Chemistry Department, Westfield College, Hampstead, London N.W.3, and not to the Postgraduate Medical School at Hammersmith.

West Cumberland Hospital

Tenders are now being invited for the main stage of the new West Cumberland Hospital. This third stage will provide, in addition to ward blocks, the theatres, *x*-ray, physiotherapy, pathology, and central sterile supply departments, out-patients department, and pharmacy, together with an accident and orthopaedic wing, including a casualty department, and a maternity hospital.

Stage 2 of the hospital, which comprises 100 beds for geriatric and medical patients, together with a psychiatric department for both in- and out-patients, has now been open for some months. Stage 1, which was the tuberculosis department, in a converted mansion, has been open for about four years. The hospital will



Model of the main block, West Cumberland Hospital.

provide services for a population of 140,000 in an area which is naturally self-contained and geographically at some distance from the nearest alternative hospital centre at Carlisle. (Architects: C. B. Pearson and Son.) Linked to the main hospital block, which has a relatively large out-patient department, are the following departments: psychiatric, geriatric, infectious diseases, tuberculosis, accidents and orthopaedic, maternity, and preconvalescent. There will be a total of 475 beds, and the whole scheme should be completed by early 1964 at a cost, including equipment, of just over £3¼m.

Middlesex Hospital Medical School Dinner

Some 320 past and present students attended the School's annual dinner at the Savoy Hotel on September 30. The chairman, Mr. J. P. MONKHOUSE, confessed that though for 30 years he had regarded himself as a Middlesex man he had received his training at a certain establishment, conveniently close to Paddington Station, of which Lord MORAN had been Dean.

Describing building developments during the year he said that the great event had been the opening of the first stage of the new medical school. The adjacent Vail's Printing Works had been acquired for a new training school, and reconstruction had been made possible by a gift of £140,000 from Major and Mrs. MACDONALD-BUCHANAN. The Children's Ward had been modernized and extended at a cost of £48,000, and an additional operating theatre costing £31,000 would be built. Professor B. W. WINDEYER, Dean, said that the acoustically perfect Edward Lewis Lecture Theatre filled a long-felt need. The Wellcome Trustees had also donated £50,000 for the construction of pharmacology research laboratories. Among the guests at the dinner were the Earl of LIMERICK, Lord MORAN, and the Medical Directors-General of the three Services.

"Sport and the Community"

The Wolfenden Committee on Sport, a small independent committee set up by the Central Council of Physical Recreation in 1957 to examine the general position of sport in Great Britain, has recently issued its report, *Sport and the*

Community. The members of the committee included Sir ARTHUR PORRITT, President of the British Medical Association. The report is obtainable from the Central Council of Physical Recreation, 6 Bedford Square, London W.C.1, price 3s. 6d., post free.

COMING EVENTS

College of General Practitioners.—Lecture and demonstration: Professor SHEILA SHERLOCK, "The Differential Diagnosis of Jaundice," October 8, 2.15 p.m., Royal Free Hospital, Grays Inn Road, London W.C.1.

Institute of Urology.—Weekend course, "Urology for Higher Examinations," October 14–16. Details on advertisement p. 64.

British Association of Sport and Medicine.—Lecture programme, October 15, 10 a.m. to 5 p.m., Arthur Stanley Institute, Peto Place, Marylebone Road, London N.W.1. Informal dinner: Horse Shoe Hotel, Tottenham Court Road, London W.1. Tickets from Dr. D. J. CUSSEN, St. Helen's Court, Great St. Helen's, London E.C.3.

Association of Clinical Biochemists (Southern Region).—Meeting, at General Hospital, Daly's Road, Rochford, Essex, October 22, 2 p.m. Members wishing to have tea should apply to Dr. P. W. PERRYMAN, at the hospital, by October 17.

International Federation of Surgical Colleges.—October 18–20, Royal College of Surgeons of England. Theme: "The Training of Surgeons." Details from Mr. KENNETH CASSELS, I.F.S.C., Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2.

B.M.A. Lecture Discussions.—An autumn and winter series mainly concerned with the handling of problems commonly encountered in practice (see annotation, p. 1077). October 20, 5.30 p.m.: Dr. PAUL WOOD, "The Selection of Cases for Cardiac Surgery," (Chairman, Sir ARTHUR THOMSON). Tea from 5 p.m. Those wishing to attend should notify Dr. W. HEDGCOCK, B.M.A. House, Tavistock Square, London W.C.1. Future meetings: December 15: Mr. H. OSMOND-CLARKE, "Fractures Around the Wrist"; January 19: Professor J. H. KELLGREN, "The Diagnosis and Treatment of Osteo-Arthritis"; March 16: Dr. MAURICE PARTRIDGE, "The Anti-Depressant Drugs."

Queen's Institute of District Nursing.—Annual meeting October 20, 2.30 p.m., Assembly Hall, Church House, Dean's Yard, Westminster, London S.W.1. Address: Sir KENNETH COWAN.

London Division, Ileostomy Association of Great Britain.—Meeting, Great Hall, B.M.A. House, October 22: 2.30 p.m., exhibition of ileostomy appliances; 3 p.m., Dr. R. W. BARTER (Princess Mary's Hospital, Margate), "Rehabilitation."

Worshipful Society of Apothecaries of London.—Annual Master's Day Service, Church of St. Mary, Aldermary, October 23, 11.15 a.m.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 10

POSTGRADUATE MEDICAL SCHOOL.—4 p.m., Professor A. C. Dornhorst: Asthma in Hospital.

Tuesday, October 11

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. F. J. Fish: Existentialism and Psychiatry.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. I. A. Magnus: Effects of Physical Agents.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. R. W. Gilliatt: New Studies of Peripheral Nerve Conduction.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Large Anatomy Theatre, Medical School, Manchester University, 7.30 for 8 p.m., Presidential Address by Mr. H. T. Simmons: On Ulcerative Colitis.

OSLER CLUB OF LONDON.—At British Museum, 8.15 p.m., subject: Sir Hans Sloane (1660-1753). Speakers, Sir Frank Francis, Dr. W. S. C. Copeman, and Mr. W. T. Stearn.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Professor Charles Wells: Urethral Injuries and the Treatment of Stricture.

ROYAL STATISTICAL SOCIETY: GENERAL APPLICATIONS SECTION.—At Royal Institute of Public Health and Hygiene, 5.45 for 6.15 p.m., Mr. W. F. F. Kemsley: Professional Earnings.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Mr. Stanley Way: Carcinoma of the Vulva (film).

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. N. G. Hulbert: Neurology.

Wednesday, October 12

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Miss Yvonne Clayton: Fungi Causing Human Disease.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. W. Riddell: Diagnosis of the Pulmonary Mycoses.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. Harland Rees: Increased Frequency of Micturition.

INSTITUTE OF NEUROLOGY.—5.30 p.m., Sir Russell Brain, Bt.: Cerebral Basis of Mind.

●LEEDS UNIVERSITY.—At General Infirmary at Leeds, (1) 5 p.m., Mr. J. B. Farquhar: Infertility. (2) 6 p.m., Mr. T. F. Redman: Pre-eclampsia.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Medical School, Manchester University, 4.30 for 5 p.m., Dr. J. L. Emery: Sudden Death in Infancy.

POSTGRADUATE MEDICAL SCHOOL.—2 p.m., Professor G. H. Lathe: Biochemical Basis of Liver-function Tests.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At General Infirmary at Leeds, 8.30 p.m., Professor J. W. Dundee: Importance of Analgesia in Anaesthesia.

Thursday, October 13

ALFRED ADLER MEDICAL SOCIETY.—At 11 Chandos Street, London W., 8 p.m., subject: Modern Trends in Individual Psychology—Reports on the recent International Congress.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. S. Pegum: Pilo-sebaceous Units. The Hair Cycle. Some Anomalies of Hair Growth.

LIVERPOOL MEDICAL INSTITUTION.—Presidential address.

ST. ANDREWS UNIVERSITY.—At Physiology Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor P. A. Owren (Oslo): Haemostasis and Thrombosis.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Hamilton Paterson: postgraduate demonstration in neurology.

Friday, October 14

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. D. Samman: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. D. Barlow: clinical demonstration.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL.—At Medical School Lecture Theatre, 4.30 p.m., 13th Thomas Percy Legg Memorial Lecture by Sir James Paterson Ross: Principles of Surgery.

LEEDS UNIVERSITY: FACULTY OF MEDICINE.—At Riley Smith Hall, University Union, 3 p.m., Inaugural Lecture by Sir Robert S. Aitken: Medicine To-day and To-morrow.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Dr. J. W. Landells: Dangers of Medical Treatment.

POSTGRADUATE MEDICAL SCHOOL.—(1) 10 a.m., Mr. Charles Drew: Some Aspects of Profound Hypothermia in Cardiac Surgery. (2) 4 p.m., Professor R. Lovell: Coronary and Hypertension Problems.

SOCIETY OF MEDICAL OFFICERS OF HEALTH: HOME COUNTIES BRANCH.—In Room 105, London School of Hygiene and Tropical Medicine, 3 p.m., Dr. G. R. S. Little: College of General Practitioners and General Practice.

SOCIETY OF MEDICAL OFFICERS OF HEALTH: METROPOLITAN BRANCH.—5.30 p.m., annual meeting. Dr. C. O. S. Blyth Brooke: Epidemiology of Lung Cancer.

YORKSHIRE THORACIC SOCIETY.—At General Infirmary at Leeds, 5.30 p.m., Sir Russell Brock: Present Position of Cardiac Surgery.

Saturday, October 15

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Norfolk and Norwich Hospital, 10.30 a.m., symposium: Haemorrhage and Shock.

●COLLEGE OF GENERAL PRACTITIONERS: NORTHERN HOME COUNTIES FACULTY.—At Barnet General Hospital, 10 a.m., Pfizer Symposium: Vomiting in Infancy and Childhood, under direction of Dr. George Newns.

Sunday, October 16

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE.—At Theatre 1, Clinical Sciences Building, York Place, Manchester, 11 a.m., in conjunction with North-west England Faculty, College of General Practitioners. Dr. H. T. Howatt and Dr. Simon Freeman: Antibiotics.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Back.—On September 17, 1960, in hospital, Harry Back, M.D., of 22 Sneath Avenue, Golders Green, London N.W.

Belt.—On September 13, 1960, at his home, Littledown, Streatley, Berks, Francis Victor Owen Belt, M.D., D.T.M.&H., Lieutenant-Colonel, I.M.S., retired, aged 86.

Bolus.—On September 17, 1960, at Victoria, British Columbia, Canada, Percy Reginald Bolus, O.B.E., M.B.

Gardner.—On September 17, 1960, in hospital, William Ross Gardner, D.S.O. (Bar), M.B., Ch.B., of Lindley House, Brierley, near Barnsley, Yorks, aged 71.

Gavin.—On September 19, 1960, Frederick William Gavin, M.D., D.P.H., of The Hawthorns, Hurgill Road, Richmond, Yorks, late of Ardnay, Trinity, Edinburgh.

Graham.—On September 18, 1960, at his home, 1 North Villas, The Spa, Gloucester, Edward O'Driscoll Graham, M.B., Ch.B.

Gregory.—On September 18, 1960, William Herbert Gregory, M.D., of Beverley, Yorks, aged 92.

Jones.—On September 8, 1960, at Llandough Hospital, Evan Gordon Jones, M.R.C.S., L.R.C.P., of Pontyclun, Glam.

Rourke.—On September 9, 1960, Joseph Michael Rourke, M.B., B.Ch., of Kensington, London W.

Shacklock.—On September 12, 1960, at his home, Yattendon, Berks, George Augustus Shelmerdine Shacklock, M.R.C.S., L.R.C.P.

Walmisley.—On September 12, 1960, in hospital, Nicholas Walmisley, L.M.S.S.A., of Clapham Park, and St. James's, London S.W., aged 91.

Watt.—On September 12, 1960, at the Royal Alexandra Infirmary, Paisley, Renfrewshire, William James Cunningham Watt, T.D., M.B., Ch.B., D.L., of 1 Riccartsbar Avenue, Paisley.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Sliding Hiatus Hernia

Q.—*An elderly man suffers from a sliding hiatus hernia. There is no x-ray evidence of ulcer or growth. After a very small feed he has oesophageal spasm and vomits even water. Nitrites do not help much and propantheline brings only a limited improvement. He is unfit for surgery. Can you suggest anything else?*

A.—It would appear that this man has a severe degree of oesophagitis secondary to his sliding hiatal hernia and reflux. It is also possible that a peptic stricture of the oesophagus has developed. If the patient is able to stand oesophagoscopy this would be most desirable, since the severity of the oesophagitis could be assessed and organic stenosis, if present, could be dilated with bougies. Such a dilatation often produces a symptomatic remission of three to six months, and can be repeated subsequently. If an oesophagoscopy is not deemed safe or desirable, I can only suggest that the patient be treated with 4 litres of milk, if necessary fortified with a concentrated food such as "casilan" or "complan," which should be dripped into the oesophagus daily through a gastric tube the tip of which is placed in the mid-oesophagus. I have found that soluble antispasmodics, such as tincture of belladonna or atropine methonitrate solution, are more effective than the newer synthetic anticholinergic drugs. These should be given in a dosage which induces slight toxic effects, since the tolerance from patient to patient varies enormously. The patient should be nursed propped up in bed or with the head of the bed raised on wooden blocks to minimize the likelihood of further regurgitation. As the oesophagitis subsides two-hourly milk feeds should be given by mouth and some solid food added later. Once free oesophageal reflux is established recurrent symptoms are very likely.

First-aid for Patients on Anticoagulants

Q.—*Some patients return to work while taking maintenance doses of anticoagulant preparations. In the event of injury causing haemorrhage would the usual first-aid measures for similar injuries to normal people be sufficient to control bleeding or should they include the administration of antidotes?*

A.—For minor injuries the usual first-aid treatment should be sufficient, but, of course, extra care should be taken over haemostasis. It is assumed that patients with major injuries would be transported to hospital immediately, and in cases involving severe haemorrhage the usual methods of controlling this would obviously take preference over the administration of antidotes to anticoagulants. The prothrombin time should be checked when the patient arrives in hospital.

Special care should be taken in the management of persons receiving non-penetrating injuries which might cause concealed internal haemorrhage. Such haemorrhage might well be aggravated in a patient on anticoagulant treatment. If, for example, a person has received a non-penetrating abdominal injury he should be kept under more meticulous observation than is usually required, and under these circumstances transfer to hospital would probably be advisable.

Future effective prolongation of prothrombin time with the coumarin type of anticoagulants may be very difficult for some time after vitamin K has been given. Furthermore, the sudden abolition of the anticoagulant effect may precipitate intravascular thrombosis. For this reason vitamin K should not be used unless really indicated. Moreover, in cases of severe haemorrhage blood transfusion is likely to be required in any event, and if fresh blood is used this will act as an effective antidote to the anticoagulants.

The risks of excessive haemorrhage due to trauma during properly controlled anticoagulant therapy are not necessarily great, for it is even possible to perform operations such as mitral valvotomy under anticoagulant cover without excessive blood loss.

Collapse after Gold Injection

Q.—*A woman aged 42 with rheumatoid arthritis collapsed and became pulseless after an injection of 0.02 g. of "myocrisin." The first injection (0.01 g.) of the course was given a week previously with no ill effects. The patient recovered after an injection of adrenaline, but was left with a homonymous hemianopia, which persists after six months. There are no other neurological signs. Has this been reported before?*

A.—Such a reaction occurring so rapidly after a second injection of myocrisin is not known to me. Such "anaphylactoid" reactions do occur, however, with many substances: the ocular complication suggests a vascular (thrombotic) complication. In my own experience, and the literature I have studied, I have not to date found a similar case.

Buerger's Disease in a Woman

Q.—*What is the present treatment for thromboanglitis obliterans (Buerger's disease) in a woman aged 57?*

A.—Thromboangiitis obliterans, or Buerger's disease, is uncommon in women, and it is almost unknown for this disease to arise after the age of 45. It seems to me, therefore, that your patient will be suffering from atherosclerosis as the cause of her symptoms, which are presumably either intermittent claudication or ischaemic symptoms in the feet.

The treatment of this abnormality is in the first instance with vasodilator drugs and reduction of smoking. Steps may also be taken, by controlling the diet, to try to limit the further development of the atherosclerosis. If these measures are not effective, it is probably wise to refer the patient to a surgeon. There are two main operations which he might perform: first, a sympathectomy designed to increase the efficiency of the collateral circulation, and, secondly, in carefully selected cases, an arterial reconstruction operation.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

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